

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
28 March 2002 (28.03.2002)

PCT

(10) International Publication Number  
**WO 02/24667 A1**

(51) International Patent Classification<sup>7</sup>: **C07D 239/94**,  
239/95, 403/12, 405/12, 409/14, 401/12, 409/04, A61K  
31/517, A61P 9/10

(21) International Application Number: PCT/EP01/10705

(22) International Filing Date:  
17 September 2001 (17.09.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
09/666,908 20 September 2000 (20.09.2000) US

(71) Applicant (for all designated States except US): **MERCK  
PATENT GMBH** [DE/DE]; Frankfurter Strasse 250,  
64293 Darmstadt (DE).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **MEDERSKI,  
Werner** [DE/DE]; Am Ohlenberg 29, 64390 Erzhausen  
(DE). **DEVANT, Ralf** [DE/DE]; Frankfurter Land-  
strasse 135, 64291 Darmstadt (DE). **BARNICKEL,  
Gerhard** [DE/DE]; Emilstrasse 27, 64298 Darmstadt  
(DE). **BERNOTAT-DANIELOWSKI, Sabine** [DE/DE];  
Liebigstrasse 5, 61231 Bad Nauheim (DE). **VICKERS,  
James** [GB/DE]; Mörikestrasse 6, 65719 Hofheim/Ts.  
(DE). **CEZANNE, Bertram** [DE/DE]; Goethestrasse  
47, 64546 Mörfelden-Walldorf (DE). **DHANO, Daljit**  
[US/US]; 2037 Skiles Blvd., West Chester, PA 19382 (US).  
**ZHAO, Bao-Ping** [CN/US]; 3606 Hunters Glen Drive,

Plainsboro, NJ 08536 (US). **RINKER, James** [US/US];  
1115 Fern Avenue, Kenhurst, PA 19607 (US). **PLAYER,  
Mark, R.** [US/US]; 5022 Swan Drive, Phoenixville, PA  
19460 (US). **JAEGER, Edward** [US/US]; 210 Kelso  
Circle, Trappe, PA 19426 (US). **SOLL, Richard** [US/US];  
324 Glenn Avenue, Lawrenceville, NJ 08648 (US).

(74) Common Representative: **MERCK PATENT GMBH**;  
Frankfurter Strasse 250, 64293 Darmstadt (DE).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,  
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,  
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,  
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,  
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,  
MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK,  
SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA,  
ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM,  
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian  
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European  
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,  
IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF,  
CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD,  
TG).

**Published:**

— with international search report

For two-letter codes and other abbreviations, refer to the "Guid-  
ance Notes on Codes and Abbreviations" appearing at the begin-  
ning of each regular issue of the PCT Gazette.

(54) Title: 4-AMINO-QUINAZOLINES

(57) Abstract: Quinazolines of the formula (I) in which R, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and Y have the meaning indicated in Patent Claim 1, and their salts or solvates as glycoprotein lbIX antagonists.

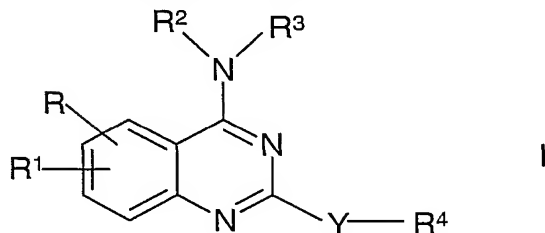


**WO 02/24667 A1**

## 4-Amino-quinazolines

The invention relates to substituted 4-amino-quinazolines of the formula I

5



in which

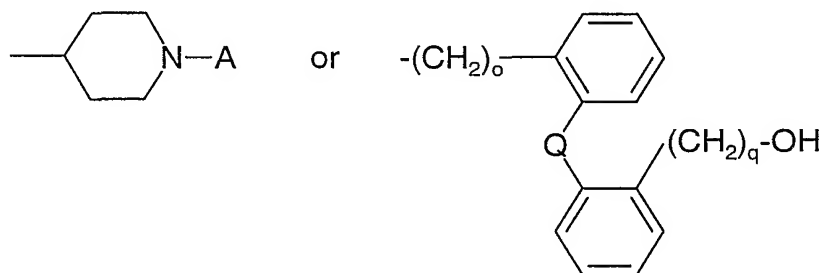
10

R and R<sup>1</sup> are independently of each other H, A, OH, OA, Hal, N(R<sup>5</sup>)<sub>2</sub>, NO<sub>2</sub>, CN, CHO, COA, CON(R<sup>5</sup>)<sub>2</sub>, COOR<sup>5</sup>, allyl, CH=CH-COOR<sup>5</sup>, CH=CHCON(R<sup>5</sup>)<sub>2</sub>, SO<sub>2</sub>A or phenyl, which is unsubstituted or mono-, di- or trisubstituted by A,

15

R<sup>2</sup> and R<sup>3</sup> are independently of each other H, A, cycloalkyl, -Het<sup>3</sup>, -(CH<sub>2</sub>)<sub>o</sub>-OR<sup>5</sup>, -(CH<sub>2</sub>)<sub>o</sub>-OR<sup>6</sup>, -(CH<sub>2</sub>)<sub>o</sub>-Het, -(CH<sub>2</sub>)<sub>o</sub>-NR<sup>5</sup>-Het, -(CHA)<sub>p</sub>-(CH<sub>2</sub>)<sub>o</sub>-N(R<sup>5</sup>)<sub>2</sub>, -(CH<sub>2</sub>)<sub>p</sub>-(CHA)<sub>p</sub>-(CH<sub>2</sub>)<sub>m</sub>-Ar, -(CH<sub>2</sub>)<sub>o</sub>-Z-(CH<sub>2</sub>)<sub>q</sub>-N(R<sup>5</sup>)<sub>2</sub>,

20



25

provided that R<sup>2</sup> and R<sup>3</sup> together are not H, or NR<sup>2</sup>R<sup>3</sup> together form a saturated monocyclic heterocyclic radical having 5 to 6 ring members, where 1 or 2 N atoms are present and the heterocyclic radical can be mono- or disubstituted by OH, Ar, OAr or arylalkyl,

30

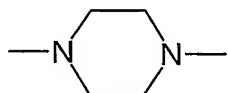
R<sup>4</sup> is Ar or Het<sup>1</sup>,  
 R<sup>5</sup> is H or A,  
 R<sup>6</sup> is benzo[1,3]dioxol-5-yl,  
 R<sup>7</sup> is H, A, cycloalkyl or -(CH<sub>2</sub>)<sub>q</sub>-OR<sup>5</sup>,

Q is O or S,

Y is a direct bond,  $(\text{CH}_2)_n$  or  $-\text{NR}^5-(\text{CH}_2)_m-$ ,

Z is phenylene, cyclohexylene,  $-\text{NR}^5-$ , O,  $-\text{CH}(\text{OH})-$ ,  $-\text{CA}_2-$  or

5



A is unbranched or branched alkyl having 1 to 6 carbon atoms,

Ar is phenyl, naphthyl or biphenyl, which is unsubstituted or mono-, di- or trisubstituted by A, OH, OA, cycloalkyloxy,  $\text{O}-(\text{CH}_2)_p\text{-Ph}$ ,  $\text{CF}_3$ ,  $\text{OCF}_3$ , Hal, CN, CHO, COA,  $\text{COOR}^5$ ,  $-(\text{CH}_2)_p\text{-N}(\text{R}^7)_2$ ,  $\text{NR}^5\text{-COA}$ ,  $\text{NO}_2$ ,  $\text{SO}_2\text{N}(\text{R}^5)_2$ , mor,  $\text{SO}_2\text{-mor}$ , 5-methyl-3-oxo-2,4-dihydropyrazol-2-yl, naphthyl or  $\text{Het}^2$ ,

10

Het is a saturated, partially or completely unsaturated mono- or bicyclic heterocyclic radical having 5 to 10 ring members, where 1 or 2 N and/or 1 or 2 S or O atoms can be present and the heterocyclic radical can be mono- or disubstituted by A, Hal, OH, OA,  $\text{CF}_3$ ,  $\text{OCF}_3$ ,  $\text{N}(\text{R}^5)_2$ , carbonyl oxygen,  $\text{COOR}^5$ , benzyl,  $\text{Het}^2$  or phenyl which is unsubstituted or mono-, di- or trisubstituted by A, OH, OA,  $\text{CF}_3$ ,  $\text{OCF}_3$ , Hal, CN,  $\text{COOR}^5$ ,  $\text{N}(\text{R}^5)_2$ ,  $\text{NO}_2$ ,  $\text{SO}_2\text{N}(\text{R}^5)_2$ ,

15

$\text{Het}^1$  is thiophen-2-yl which is substituted by Ar or  $\text{Het}^2$ ,

$\text{Het}^2$  is a unsaturated mono- or bicyclic heterocyclic radical having 5 to 10 ring members, where 1 or 2 N and/or 1 or 2 S or O atoms can be present and the heterocyclic radical can be mono- or disubstituted by A, Hal, OH, OA,  $\text{CF}_3$ ,  $\text{OCF}_3$ ,  $\text{N}(\text{R}^5)_2$ ,  $-(\text{CH}_2)_p\text{-(CHA)}_p\text{-N}(\text{R}^5)\text{-(CH}_2)_q\text{-COR}^5$ , CHO, COA or  $\text{COOR}^5$ ,

20

25

$\text{Het}^3$  is a partially or completely unsaturated mono- or bicyclic heterocyclic radical having 5 to 10 ring members, where 1 or 2 N atoms are present and the heterocyclic radical can be mono- or disubstituted by A, Hal, OH, OA,  $\text{CF}_3$ ,  $\text{OCF}_3$ ,  $\text{N}(\text{R}^5)_2$ ,  $\text{SO}_2\text{A}$  or  $\text{COOR}^5$  provided that the heterocyclic radical is not bonded via an N atom,

30

Hal is F, Cl, Br or I,  
mor is morpholin-4-yl,  
Ph is phenyl,  
n is 1, 2, 3, 4, 5 or 6,  
5 m is 0, 1, 2, 3, 4, 5 or 6,  
o is 1, 2, 3, 4, 5, 6 or 7,  
p is 0, 1, 2, 3 or 4,  
q is 1, 2, 3 or 4,

and their pharmaceutically tolerable salts and solvates.

10

Similar 4-amino substituted quinazolines are disclosed in WO 99/09986, Mastafanova, Li et al, Khim.-Farm.Zh. 1982, 16, 938-42, US 5,436,233 or DE 2135172.

15

The invention is based on the object of finding novel compounds having valuable properties, in particular those which can be used for the production of medicaments.

It has been found that the compounds of the formula I and their salts or solvates have very valuable pharmacological properties together with good tolerability.

20

They act especially as GPIbIX inhibitors, in particular inhibiting the interaction of this receptor with the ligand von Willebrand factor (vWF). This action can be demonstrated, for example, by a method which is described by S. Meyer et al. in J. Biol. Chem. 1993, 268, 20555-20562. The property as GPIbIX alpha-thrombin receptor (N.J. Greco, Biochemistry 1996, 35, 915-921) can also be blocked by the compounds mentioned.

25

The significance of GPIbIX as an adhesion receptor on platelets, which mediates the primary interaction of platelets with an arteriosclerotically modified vascular wall via binding to the vWF expressed there, has been described by many authors (e.g. Z.M. Ruggeri in Thromb. Hemost. 1997, 78, 611-616). The activation of another platelet adhesion receptor,

30

GPIIb/IIIa, following the GPIbIX-vWF interaction, leads to platelet aggregation and thus to thrombotic vascular occlusion.

5 A GPIbIX antagonist can thus prevent the start of thrombus formation and thus also release of active substances from the platelets which, for example, promote thrombus growth and have an additional trophic action on the vascular wall. This has been shown with inhibitory peptides or antibodies in various experimental models (e.g. H Yamamoto et al., Thromb. Hemost. 1998, 79, 202-210).

10

In the case of higher shear forces, the blocking action of GPIbIX inhibitors exerts its maximum effect, as described by J.J. Sixma et al. in Arteriosclerosis, Thrombosis, and Vascular Biology 1996, 16, 64-71. According to the flow chamber method used there, the compounds of the formula I can be characterized as GPIbIX inhibitors in whole blood.

15

The inhibition of thrombus formation of the GPIbIX inhibitors can be measured by a modified Born method (Nature 1962, 4832, 927-929) using botrocetin or ristocetin as an aggregation stimulant.

20

The compounds of the formula I according to the invention can therefore be employed as pharmaceutical active compounds in human and veterinary medicine. They act as adhesion receptor antagonists, in particular as glycoprotein IbIX antagonists, and are suitable for the prophylaxis and/or therapy of thrombotic disorders and sequelae deriving therefrom. The preferentially best action is to be expected in the case of thrombotic disorders in the arterial vascular system, but GPIbIX inhibitors also have an effect in the case of thrombotic disorders in the venous vascular bed. The disorders are acute coronary syndromes, angina pectoris, myocardial infarct, peripheral circulatory disorders, stroke, transient ischaemic attacks, arteriosclerosis, reocclusion/restenosis after angioplasty/stent implantation. The compounds can furthermore be

25

30

employed as anti-adhesive substances where the body comes into contact with foreign surfaces such as implants, catheters or cardiac pacemakers.

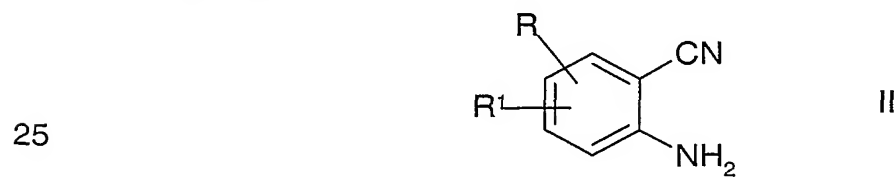
Therefore, the invention relates further to compounds of the formula I  
 5 according to Claim 1 and their physiologically acceptable salts or solvates as pharmaceutical active compounds.

The invention relates to compounds of the formula I according to Claim 1  
 10 and their physiologically acceptable salts or solvates as glycoprotein IbIX antagonists.

Comparison medication introduced onto the market which may be mentioned are aspirin and GPIIbIIIa antagonists.

15 The invention relates to the compounds of the formula I and their salts or solvates, and to a process for the preparation of these compounds and their salts or solvates, characterized in that

- a) a compound of the formula I is liberated from one of its functional derivatives by treating with a solvolysing or hydrogenolysing agent,  
 20 or  
 b) for compounds in which Y is a direct bond or  $(CH_2)_n$  in stage 1) a compound of the formula II



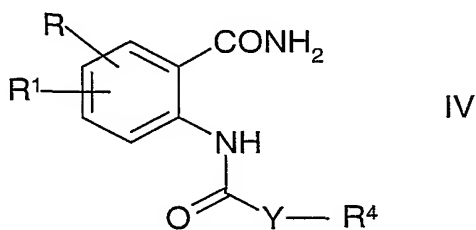
in which

R and R<sup>1</sup> have a meaning indicated in Claim 1,  
 is reacted with a compound of the formula III



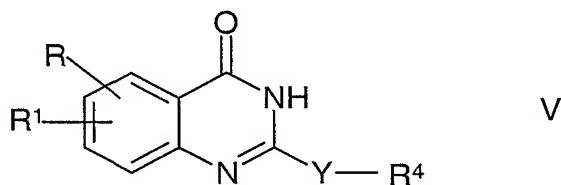
in which  $R^4$  has a meaning indicated in Claim 1 and Y is a direct bond or  $(CH_2)_n$ ,

and X is Cl, Br, OH or a reactive esterified OH group followed by converting the cyano group to an amide group by conventional means to give a compound of formula IV



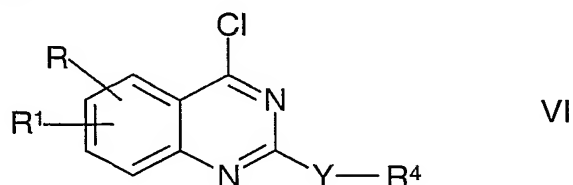
in which R,  $R^1$  and  $R^4$  have a meaning indicated in Claim 1 and Y is a direct bond or  $(CH_2)_n$ ,

in stage 2) a compound of formula IV as indicated above is reacted with a base to give a compound of formula V



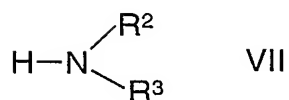
in which R,  $R^1$  and  $R^4$  have a meaning indicated in Claim 1 and Y is a direct bond or  $(CH_2)_n$ ,

in stage 3) a compound of formula V as indicated above is reacted with a chlorinating agent to give a compound of formula VI



in which R,  $R^1$  and  $R^4$  have a meaning indicated in Claim 1 and Y is a direct bond or  $(CH_2)_n$ ,

and in stage 4) a compound of formula VI as indicated above is reacted with a compound of formula VII

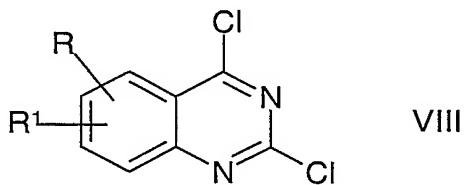


in which  $\text{R}^2$  and  $\text{R}^3$  or  $\text{NR}^2\text{R}^3$  have a meaning indicated in Claim 1,

or

b) for compounds in which Y is  $\text{NR}^5-(\text{CH}_2)_m-$ ,

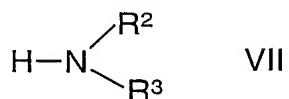
in stage 1) a compound of the formula VIII



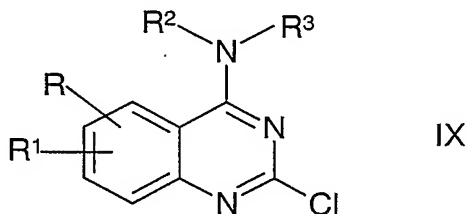
in which

$\text{R}$  and  $\text{R}^1$  have a meaning indicated in Claim 1,

is reacted with a compound of formula VII



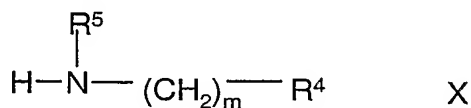
in which  $\text{R}^2$  and  $\text{R}^3$  or  $\text{NR}^2\text{R}^3$  have a meaning indicated in Claim 1, to give a compound of formula IX



in which  $\text{R}$ ,  $\text{R}^1$ ,  $\text{R}^2$ ,  $\text{R}^3$  and  $\text{NR}^2\text{R}^3$  have a meaning indicated in Claim 1,

and

in stage 2) a compound of formula IX as indicated above is reacted with a compound of formula X



in which  $\text{R}^4$ ,  $\text{R}^5$  and  $m$  have a meaning indicated in Claim 1

or

d) a radical R, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and/or R<sup>4</sup> is converted into another radical R, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and/or R<sup>4</sup> by, for example

- reducing a nitro group, sulfonyl group or sulfoxyl group,
  - etherifying an OH group or subjecting an OA group to ether cleavage,
  - alkylating a primary or secondary amino group,
  - partially or completely hydrolysing a CN group,
  - cleaving an ester group or esterifying a carboxylic acid radical,
  - reacting an aryl bromide, aryl iodide, heteroaryl bromide or heteroaryliodide to give the corresponding coupling products by means of a Suzuki coupling with boronic acids,
  - reacting a iodoquinazoline or bromoquinazoline to give the corresponding coupling products by means of a Stille coupling with allyltributyltin,
  - reacting a iodoquinazoline or bromoquinazoline to give the corresponding coupling products by means of a Heck coupling with acrylates,
  - or carrying out a nucleophilic or electrophilic substitution,
- or

a base or acid of the formula I is converted into one of its salts or solvates.

The compounds of the formula I can have a chiral center and therefore occur in a number of stereoisomeric forms. All these forms (e.g. R and S forms) and their mixtures (e.g. the RS forms) are included in the formula I.

The compounds according to the invention also include so-called prodrug derivatives, i.e. compounds of the formula I modified with, for example, alkyl or acyl groups, sugars or oligopeptides and which are rapidly cleaved in the body to give the active compounds according to the invention.

Furthermore, free amino groups as substituents of compounds of the formula I can be provided with appropriate conventional protective groups.

Solvates of the compounds of the formula I are understood as meaning adducts of inert solvent molecules to the compounds of the formula I which are formed on account of their mutual power of attraction. Solvates are, for example, mono- or dihydrates or alcoholates.

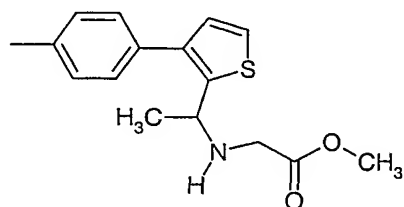
5

The abbreviations used have the following meanings:

- |    |      |                                       |
|----|------|---------------------------------------|
|    | Ac   | acetyl,                               |
|    | Bu   | n-butyl,                              |
|    | DBU  | 1,8-diazabicyclo[5.4.0]undec-7-ene,   |
| 10 | DMA  | dimethylacetamide,                    |
|    | DMF  | dimethylformamide,                    |
|    | dppf | 1,1'-bis(diphenylphosphino)ferrocene, |
|    | Et   | ethyl,                                |
|    | iPr  | isopropyl,                            |
| 15 | Me   | methyl,                               |
|    | Ph   | phenyl,                               |
|    | TEA  | triethylamine,                        |
|    | TFA  | trifluoroacetic acid.                 |
- 20 In the above formulae, A is alkyl and has 1 to 6, preferably 1, 2, 3 or 4 C atoms. Alkyl is preferably methyl, furthermore ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl or tert-butyl, additionally also pentyl, 1-, 2- or 3-methylbutyl, 1,1-, 1,2- or 2,2-dimethylpropyl, 1-ethylpropyl, hexyl, 1-, 2-, 3- or 4-methylpentyl, 1,1-, 1,2-, 1,3-, 2,2-, 2,3- or 3,3-dimethylbutyl, 1- or 2-ethylbutyl, 1-ethyl-1-methylpropyl, 1-ethyl-2-methylpropyl, 1,1,2- or 1,2,2-trimethylpropyl.
- A is preferentially methyl, ethyl, propyl, isopropyl, butyl or pentyl.

30 Ar is phenyl, naphthyl or biphenyl, which is unsubstituted or mono-, di- or trisubstituted by A, OH, OA, cycloalkyloxy, O-(CH<sub>2</sub>)<sub>p</sub>-Ph, CF<sub>3</sub>, OCF<sub>3</sub>, Hal, CN, CHO, COA, COOR<sup>5</sup>, -(CH<sub>2</sub>)<sub>p</sub>-N(R<sup>7</sup>)<sub>2</sub>, NR<sup>5</sup>-COA, NO<sub>2</sub>, SO<sub>2</sub>N(R<sup>5</sup>)<sub>2</sub>, mor, SO<sub>2</sub>-mor, 5-methyl-3-oxo-2,4-dihydropyrazol-2-yl, naphthyl or Het<sup>2</sup>.

Ar is preferentially phenyl, preferably - as indicated - mono- di- or trisubstituted phenyl, specifically preferentially phenyl, 2-, 3- or 4-methylphenyl, 2-, 3- or 4-ethylphenyl, 2-, 3- or 4-propylphenyl, 2-, 3- or 4-isopropylphenyl, 2-, 3- or 4-butylphenyl, 2-, 3- or 4-tert-butylphenyl, 2-, 3- or 4-aminophenyl, 2-, 3- or 4-N,N-dimethylaminophenyl, 2-, 3- or 4-sulfamoylphenyl, 2-, 3- or 4-nitrophenyl, 2-, 3- or 4-hydroxyphenyl, 2-, 3- or 4-methoxyphenyl, 2-, 3- or 4-ethoxyphenyl, 2-, 3- or 4-pentoxyphe-  
 5 nyl, 2-, 3- or 4-phenoxyphenyl, 2-, 3- or 4-phenylmethoxyphenyl, 2-, 3- or 4-trifluoromethylphenyl, 2-, 3- or 4-trifluoromethoxyphenyl, 2-, 3- or 4-cyclopentyloxyphenyl, 2-, 3- or 4-carboxyphenyl, 2-, 3- or 4-(N,N-diethyl)sulfamoylphenyl, 4-(3-methyl-butyramido)-phenyl, 2-, 3- or 4-cyanophenyl, 2-, 3- or 4-fluorophenyl, 2-, 3- or 4-chlorophenyl, 2-, 3- or 4-bromophenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dichlorophenyl, 2,3-, 2,4-,  
 10 2,5-, 2,6-, 3,4- or 3,5-dibromophenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dimethoxyphenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-di(trifluoromethyl)phenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-di(phenylmethoxy)phenyl, 2-chloro-6-methylphenyl, 2-chloro-4-fluorophenyl, 3-bromo-6-fluorophenyl, 3,4,5-trimethoxyphenyl, 4-(morpholin-4-yl)phenyl, 4-(morpholin-4-yl-  
 15 sulfonyl)phenyl, 4-(5-methyl-3-oxo-2,4-dihydropyrazol-2-yl)phenyl, 4-(4,6-dimethoxy-pyrimidin-2-yl)phenyl, 3-(4,6-dimethoxy-pyrimidin-2-yl)phenyl, 4-(pyrid-3-yl)phenyl, 3-(pyrid-3-yl)phenyl, 4-(thiophen-2-yl)phenyl, 4-(thiophen-3-yl)phenyl, 4-(2-formyl-thiophen-3-yl)phenyl, 3-(thiophen-2-yl)phenyl, 4-(benzo[c]thiophen-2-yl)phenyl, 4-(naphthalen-1-yl)phenyl or



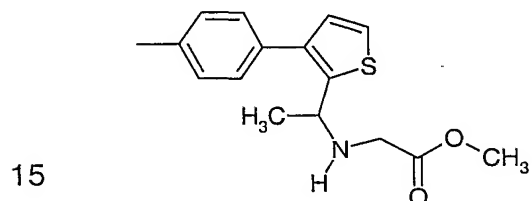
30 Furthermore, however, Ar is also preferentially unsubstituted naphthyl or biphenyl - as indicated - or alternatively mono-, di- or trisubstituted

biphenyl, specifically preferentially biphenyl-4-yl or biphenyl-3-yl,  
2'-methylbiphenyl-4-yl, 3'-methylbiphenyl-4-yl, 4'-methylbiphenyl-4-yl,  
2'-methylbiphenyl-3-yl, 3'-methylbiphenyl-3-yl, 4'-methylbiphenyl-3-yl,  
2-methylbiphenyl-4-yl, 3-methylbiphenyl-4-yl, 2-methylbiphenyl-3-yl,  
5 4-methylbiphenyl-3-yl, 2'-tert-butylbiphenyl-4-yl, 3'-tert-butylbiphenyl-4-yl,  
4'-tert-butylbiphenyl-4-yl, 2'-tert-butylbiphenyl-3-yl, 3'-tert-butylbiphenyl-3-yl,  
4'-tert-butylbiphenyl-3-yl, 2-tert-butylbiphenyl-4-yl, 3-tert-butylbiphenyl-4-yl,  
2-tertbutylbiphenyl-3-yl, 4-tert-butylbiphenyl-3-yl, 2'-isopropylbiphenyl-4-yl,  
3'-isopropylbiphenyl-4-yl, 4'-isopropylbiphenyl-4-yl, 2'-isopropylbiphenyl-3-  
10 yl, 3'-isopropylbiphenyl-3-yl, 4'-isopropylbiphenyl-3-yl, 2-isopropylbiphenyl-  
4-yl, 3-isopropylbiphenyl-4-yl, 2-isopropylbiphenyl), 4-isopropylbiphenyl-3-  
yl, 2'-fluorobiphenyl-4-yl, 3'-fluorobiphenyl-4-yl, 4'-fluorobiphenyl-4-yl,  
2'-fluorobiphenyl-3-yl, 3'-fluorobiphenyl-3-yl, 4'-fluorobiphenyl-3-yl,  
2-fluorobiphenyl-4-yl, 3-fluorobiphenyl-4-yl, 2-fluorobiphenyl-3-yl, 4-fluoro-  
15 biphenyl-3-yl, 2'-chlorobiphenyl-4-yl, 3'-chlorobiphenyl-4-yl, 4'-chloro-  
biphenyl-4-yl, 2'-chlorobiphenyl-3-yl, 3'-chlorobiphenyl-3-yl,  
4'-chlorobiphenyl-3-yl, 2-chlorobiphenyl-4-yl, 3-chlorobiphenyl-4-yl,  
2-chlorobiphenyl-3-yl, 4-chlorobiphenyl-3-yl, 2'-methoxybiphenyl-4-yl,  
3'-methoxybiphenyl-4-yl, 4'-methoxybiphenyl-4-yl, 2'-methoxybiphenyl-3-yl,  
20 3'-methoxybiphenyl-3-yl, 4'-methoxybiphenyl-3-yl, 2-methoxybiphenyl-4-yl,  
3-methoxybiphenyl-4-yl, 2-methoxybiphenyl-3-yl, 4-methoxybiphenyl-3-yl,  
2'-nitrobiphenyl-4-yl, 3'-nitrobiphenyl-4-yl, 4'-nitrobiphenyl-4-yl, 2'-nitro-  
biphenyl-3-yl, 3'-nitrobiphenyl-3-yl, 4'-nitrobiphenyl-3-yl, 2-nitrobiphenyl-4-yl,  
3-nitrobiphenyl-4-yl, 2-nitrobiphenyl-3-yl, 4-nitrobiphenyl-3-yl,  
25 2'-trifluoromethylbiphenyl-4-yl, 3'-trifluoromethylbiphenyl-4-yl, 4'-tri-  
fluoromethyl-biphenyl-4-yl, 2'-trifluoromethylbiphenyl-3-yl,  
3'-trifluoromethylbiphenyl-3-yl, 4'-trifluoromethylbiphenyl-3-yl,  
2-trifluoromethylbiphenyl-4-yl, 3-trifluoromethylbiphenyl-4-yl,  
2-trifluoromethylbiphenyl-3-yl, 4-trifluoromethylbiphenyl-3-yl,  
30 2'-trifluoromethoxybiphenyl-4-yl, 3'-trifluoromethoxybiphenyl-4-yl, 4'-tri-  
fluoromethoxybiphenyl-4-yl, 2'-trifluoromethoxybiphenyl-3-yl,

3'-trifluoromethoxybiphenyl-3-yl, 4'-trifluoromethoxybiphenyl-3-yl,  
2-trifluoromethoxybiphenyl-4-yl, 3-trifluoromethoxybiphenyl-4-yl,  
2-trifluoromethoxybiphenyl-3-yl, 4-trifluoromethoxybiphenyl-3-yl, 3'-  
acetylphenyl-4-yl, 3'-acetaminobiphenyl-4-yl, 3'-aminobiphenyl-4-yl, 3'-  
5 formylbiphenyl-4-yl, 4'-formylbiphenyl-4-yl, 4'-propylaminomethylbiphenyl-4-  
yl, 3'-methoxyethylaminomethylbiphenyl-4-yl, 4'-  
cyclohexylmethylaminomethylbiphenyl-4-yl or 3'-  
hydroxypropylaminomethylbiphenyl-4-yl, furthermore preferentially  
disubstituted biphenyls, such as 2'-methyl-3'-nitrobiphenyl-4-yl, 2'-methyl-4'-  
10 nitrobiphenyl-4-yl, 2'-methyl-5'-nitrobiphenyl-4-yl, 2'-methyl-6'-nitrobiphenyl-  
4-yl, 3'-methyl-2'-nitrobiphenyl-4-yl, 3'-methyl-4'-nitrobiphenyl-4-yl,  
3'-methyl-5'-nitrobiphenyl-4-yl, 3'-methyl-6'- nitrobiphenyl-4-yl, 4'-methyl-2'-  
nitrobiphenyl-4-yl, 4'-methyl-3'-nitrobiphenyl-4-yl, 2'-methyl-3'-nitrobiphenyl-  
3-yl, 2'-methyl-4'-nitrobiphenyl-3-yl, 2'-methyl-5'-nitrobiphenyl-3-yl,  
15 2'-methyl-6'-nitrobiphenyl-3-yl, 3'-methyl-2'-nitrobiphenyl-3-yl, 3'-methyl-4'-  
nitrobiphenyl-3-yl, 3'-methyl-5'-nitrobiphenyl-3-yl, 3'-methyl-6'-nitrobiphenyl-  
3-yl, 4'-methyl-2'-nitrobiphenyl-3-yl, 4'-methyl-3'-nitrobiphenyl-3-yl, 2'-  
methoxy-2-methylbiphenyl-4-yl, 3'-methoxy-2-methylbiphenyl-4-yl,  
4'-methoxy-2-methylbiphenyl-4-yl, 4'-methoxy-3-nitrobiphenyl-4-yl,  
20 2'-chloro-3'-fluorobiphenyl-4-yl, 2'-chloro-4'- fluorobiphenyl-4-yl, 2'-chloro-5'-  
fluorobiphenyl-4-yl, 2'-chloro-6'-fluorobiphenyl-4-yl, 3'-chloro-2'-  
fluorobiphenyl-4-yl, 3'-chloro-4'-fluorobiphenyl-4-yl, 3'-chloro-5'-  
fluorobiphenyl-4-yl, 3'-chloro-6'-fluorobiphenyl-4-yl, 4'-chloro-2'-fluoro-  
biphenyl-4-yl, 4'-chloro-3'-fluorobiphenyl-4-yl, 2'-chloro-3'-fluorobiphenyl-3-  
25 yl, 2'-chloro-4'-fluorobiphenyl-3-yl, 2'-chloro-5'-fluorobiphenyl-3-yl, 2'-chloro-  
6'-fluorobiphenyl-3-yl, 3'-chloro-2'-fluorobiphenyl-3-yl, 3'-chloro-4'-fluoro-  
biphenyl-3-yl, 3'-chloro-5'-fluorobiphenyl-3-yl, 3'-chloro-6'-fluorobiphenyl-3-  
yl, 4'-chloro-2'-fluorobiphenyl-3-yl, 4'-chloro-3'- fluorobiphenyl-3-yl,  
(2,3'-diethyl)biphenyl-4-yl, (3,3'-diethyl)biphenyl-4-yl), (2,2'-diethyl)biphenyl-  
30 4-yl, (2,4'-diethyl)biphenyl-4-yl, (2',3'-dimethoxy)biphenyl-4-yl, (2',4'-  
dimethoxy)biphenyl-4-yl, (2',5'-dimethoxy)biphenyl-4-yl, (2',6'-dimethoxy)-  
biphenyl-4-yl, (3',4'-dimethoxy)biphenyl-4-yl, (3',5'-dimethoxy)biphenyl-4-yl,

- (2',3'-dimethoxy)-biphenyl-3-yl, (2',4'-dimethoxy)biphenyl-3-yl,  
 (2',5'-dimethoxy)biphenyl-3-yl, (2',6'-dimethoxy)-biphenyl-3-yl,  
 (3',4'-dimethoxy)biphenyl-3-yl, (3',5'-dimethoxy)biphenyl-3-yl,  
 (3',5'-dichloro)biphenyl-4-yl, (3',5'-dichloro)biphenyl-3-yl,  
 5 (2',4'-dichloro)biphenyl-4-yl, (3',4',5'-trimethoxy)biphenyl-4-yl,  
 (2',3'-di(trifluoromethyl))biphenyl-4-yl, (2',4'-di(trifluoromethyl))biphenyl-4-yl,  
 (2',5'-di(trifluoromethyl))biphenyl-4-yl, (2',6'-di(trifluoromethyl))biphenyl-4-yl,  
 (3',4'-di(trifluoromethyl))biphenyl-4-yl, (3',5'-di(trifluoromethyl))biphenyl-4-yl,  
 (2',3'-di(trifluoromethyl))biphenyl-3-yl, (2',4'-di(trifluoromethyl))biphenyl-3-yl,  
 10 (2',5'-di(trifluoromethyl))biphenyl-3-yl, (2',6'-di(trifluoromethyl))biphenyl-3-yl,  
 (3',4'-di(trifluoromethyl))biphenyl-3-yl, (3',5'-di(trifluoromethyl))biphenyl-3-yl,  
 (2,2'-dimethyl)biphenyl-4-yl, (2,3'-dimethyl)biphenyl-4-yl,  
 (2,4'-dimethyl)biphenyl-4-yl, (2,2'-dimethyl)biphenyl-3-yl,  
 (2,3'-dimethyl)biphenyl-3-yl or (2,4'-dimethyl)biphenyl-3-yl.
- 15 Phenyl, 2-, 3- or 4-fluorophenyl, 2-, 3- or 4-chlorophenyl, 4-bromophenyl,  
 2,4- or 3,4-dichlorophenyl, 2,5- or 3,4-dimethoxyphenyl, 3,5-bis-  
 (trifluoromethyl)phenyl, 4-aminophenyl, 4-dimethylaminophenyl, 2-, 3- or  
 4-methylphenyl, 2-, 3- or 4-methoxyphenyl, 4-propylphenyl,  
 20 4-isopropylphenyl, 4-butylphenyl, 4-tert.-butylphenyl, 2-, 3- or 4-nitrophenyl,  
 2-cyanophenyl, 2-, 3- or 4-pentoxyphenyl, 3- or 4-phenoxyphenyl, 2- or  
 4-benzyloxyphenyl, 2-, 3- or 4-trifluoromethylphenyl, 2-, 3- or 4-  
 trifluoromethoxyphenyl, 2- or 4-cyclopentyloxyphenyl, 3- or 4-  
 carboxyphenyl, 2-, 3- or 4-(N,N-diethyl)sulfamoylphenyl, 3,4-  
 25 di(benzyloxy)phenyl, 4-(3-methyl-butyramido)-phenyl, 2-chloro-6-  
 methylphenyl, 2-chloro-4-fluorophenyl, 3-bromo-6-fluorophenyl, 3,4,5-  
 trimethoxyphenyl, 4-(morpholin-4-yl)phenyl, 4-(morpholin-4-yl-  
 sulfonyl)phenyl, 4-(5-methyl-3-oxo-2,4-dihydropyrazol-2-yl)phenyl, 4-(4,6-  
 dimethoxy-pyrimidin-2-yl)phenyl, 3-(4,6-dimethoxy-pyrimidin-2-yl)phenyl, 4-  
 30 (pyridin-3-yl)phenyl, 3-(pyridin-3-yl)phenyl, 4-(thiophen-2-yl)phenyl, 3-  
 (thiophen-2-yl)phenyl, 4-(benzo[c]thiophen-2-yl)phenyl, 4-(naphthalen-1-  
 yl)phenyl, 4-(thiophen-3-yl)phenyl, 4-(2-formyl-thiophen-3-yl)phenyl,

naphthyl, biphenyl-4-yl, 2'-fluorobiphenyl-4-yl, 4'-fluorobiphenyl-4-yl, 4'-fluorobiphenyl-3-yl, 4'-chlorobiphenyl-4-yl, 4'-chlorobiphenyl-3-yl, 4'-methoxybiphenyl-4-yl, 4'-methoxybiphenyl-3-yl, 3'-nitrobiphenyl-4-yl, 3'-acetylbiphenyl-4-yl, 3'-acetaminobiphenyl-4-yl, 3'-aminobiphenyl-4-yl, 3'-formylbiphenyl-4-yl, 4'-formylbiphenyl-4-yl, 4'-propylaminomethylbiphenyl-4-yl, 3'-methoxyethyl-aminomethylbiphenyl-4-yl, 4'-cyclohexylmethyl-aminomethylbiphenyl-4-yl, 3'-hydroxypropylaminomethylbiphenyl-4-yl, (2,3'-diethyl)biphenyl-4-yl, (2,4'-diethyl)biphenyl-4-yl, (2,2'-diethyl)biphenyl-4-yl, (3',5'-dichloro)biphenyl-3-yl, (3',4'-dimethoxy)biphenyl-4-yl, (2',4'-dichloro)biphenyl-4-yl, (3',4',5'-trimethoxy)biphenyl-4-yl, (3',5'-di(trifluoromethyl))biphenyl-4-yl or



is particularly preferred for Ar.

Arylalkyl is preferentially benzyl.

20 O-(CH<sub>2</sub>)<sub>p</sub>-Ph is phenylalkyloxy, in which p can be 0, 1, 2, 3 or 4. Benzyloxy or phenyloxy is particularly preferred.

Cycloalkyl preferably has 3-7 C atoms and is preferably cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, and further also cyclopentylmethyl, cyclopentylethyl or cyclohexylmethyl; cyclopentyl, cyclohexylmethyl or cyclohexyl are particularly preferred.

25

Hal is preferably F, Cl, Br or I.

30 Het is a saturated, partially or completely unsaturated mono- or bicyclic heterocyclic radical having 5 to 10 ring members, where 1 or 2 N and/or 1 or 2 S or O atoms can be present and the heterocyclic radical can be

mono- or disubstituted by A, Hal, OH, OA, CF<sub>3</sub>, OCF<sub>3</sub>, N(R<sup>5</sup>)<sub>2</sub>, carbonyl oxygen, COOR<sup>5</sup>, Het<sup>2</sup>, benzyl or phenyl which is unsubstituted or mono-, di- or trisubstituted by A, OH, OA, CF<sub>3</sub>, OCF<sub>3</sub>, Hal, CN, COOR<sup>5</sup>, N(R<sup>5</sup>)<sub>2</sub>, NO<sub>2</sub>, SO<sub>2</sub>N(R<sup>5</sup>)<sub>2</sub>.

5

Het is preferably unsubstituted 2- or 3-furyl, 2- or 3-thiophenyl, 1-, 2- or 3-pyrrolyl, 1-, 2-, 4- or 5-imidazolyl, 1-, 3-, 4- or 5-pyrazolyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isoxazolyl, 2-, 4- or 5-thiazolyl, 3-, 4- or 5-isothiazolyl, 2-, 3- or 4-pyridyl, 2-, 4-, 5- or 6-pyrimidinyl, furthermore  
 10 preferably 1,2,3-triazol-1-, -4- or -5-yl, 1,2,4-triazol-1-, -4- or -5-yl, 1- or 5-tetrazolyl, 1,2,3-oxadiazol-4- or -5-yl, 1,2,4-oxadiazol-3- or -5-yl, 1,3,4-thiadiazol-2- or -5-yl, 1,2,4-thiadiazol-3- or -5-yl, 1,2,3-thiadiazol-4- or -5-yl, 2-, 3-, 4-, 5- or 6-2H-thiopyranyl, 2-, 3- or 4-4H-thiopyranyl, 3- or 4-pyridazinyl, pyrazinyl, 2-, 3-, 4-, 5-, 6- or  
 15 7-benzofuryl, 2-, 3-, 4-, 5-, 6- or 7-benzothiophenyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-1H-indolyl, 1-, 2-, 4- or 5-benzimidazolyl, 1-, 3-, 4-, 5-, 6- or 7-benzopyrazolyl, 2-, 4-, 5-, 6- or 7-benzoxazolyl, 3-, 4-, 5-, 6- or 7-benzisoxazolyl, 2-, 4-, 5-, 6- or 7-benzothiazolyl, 2-, 4-, 5-, 6- or 7-benzisothiazolyl, 4-, 5-, 6- or 7-benz-2,1,3-oxadiazolyl, 1-, 2-, 3-, 4-,  
 20 5-, 6-, 7- or 8-quinolyl, 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolyl, 1-, 2-, 3-, 4- or 9-carbazolyl, 1-, 2-, 3-, 4-, 5-, 6-, 7-, 8- or 9-acridinyl, 3-, 4-, 5-, 6-, 7- or 8-cinnolyl, 2-, 4-, 5-, 6-, 7- or 8-quinazolinyl. The heterocyclic radicals can also be partially or completely hydrogenated. Het can thus also be 2,3-dihydro-2-, -3-, -4- or -5-furyl, 2,5-dihydro-2-,  
 25 -3-, -4- or -5-furyl, tetrahydro-2- or -3-furyl, 1,3-dioxolan-4-yl, tetrahydro-2- or -3-thiophenyl, 2,3-dihydro-1-, -2-, -3-, -4- or -5-pyrrolyl, 2,5-dihydro-1-, -2-, -3-, -4- or -5-pyrrolyl, 1-, 2- or 3-pyrrolidinyl, tetrahydro-1-, -2- or -3-pyrrolyl, tetrahydro-1-, -2- or 4-imidazolyl, 2,3-dihydro-1-, -2-, -3-, -4-, -5-, -6-, -7-1H-indolyl,  
 30 2,3-dihydro-1-, -2-, -3-, -4- or -5-pyrazolyl, tetrahydro-1-, -3- or -4-pyrazolyl, 1,4-dihydro-1-, -2-, -3- or -4-pyridyl, 1,2,3,4-tetrahydro-1-, -2-, -3-, -4-, -5- or -6-pyridyl,

1,2,3,6-tetrahydro-1-, -2-, -3-, -4-, -5- or -6-pyridyl, 1-, 2-, 3- or 4-piperidinyl, 1-, 2-, 3- or 4-azepanyl, 2-, 3- or 4-morpholinyl, tetrahydro-2-, -3- or -4-pyranyl, 1,4-dioxanyl, 1,3-dioxan-2-, -4- or -5-yl, hexahydro-1-, -3- or -4-pyridazinyl, hexahydro-1-, -2-, -4- or -5-pyrimidinyl, 1-, 2- or 3-piperazinyl, 1,2,3,4-tetrahydro-1-, -2-, -3-, -4-, -5-, -6-, -7- or -8-quinolinyl, 1,2,3,4-tetrahydro-1-, -2-, -3-, -4-, -5-, -6-, -7- or -8-isoquinolinyl which can be substituted as indicated above or particularly substituted by A, OA, carbonyl oxygen, NO<sub>2</sub>, Het<sup>2</sup> or phenyl which is substituted by Hal, CN or OA.

10

Thiophen-2-yl, tetrahydro-furan-2-yl, 1-methyl-octahydro-indol-3-yl, benzo[1,3]dioxol-5-yl, piperazin-1-yl, 4-methyl-piperazin-1-yl, piperidin-1-yl, piperidin-4-yl, 1-methyl-piperidin-3-yl, 4-benzyl-piperidin-1-yl, 2-methyl-piperidin-1-yl, 1-ethyl-pyrrolidin-2-yl, 1-methyl-pyrrolidin-2-yl, 2-oxo-pyrrolidin-1-yl, pyridin-2-yl, pyridin-4-yl, 5-nitro-pyridin-2-yl, imidazol-1-yl, morpholin-4-yl, 5-methoxy-1H-indol-2-yl is particularly preferred for Het.

15

Het<sup>1</sup> is thiophen-2-yl which is substituted by Ar or Het<sup>2</sup>, in which Ar and Het<sup>2</sup> have one of the above or below mentioned meanings. 5-(4-Fluorophenyl)-thiophen-2-yl, 5-(2-methoxyphenyl)-thiophen-2-yl, 5-(2-cyanophenyl)-thiophen-2-yl, 5-(2,5-dimethoxyphenyl)-thiophen-2-yl, 2-[2,2']bithiophenyl-5-yl, 5-(pyridin-4-yl)-thiophen-2-yl, 5-(1H-indol-5-yl)-thiophen-2-yl, 5-quinolin-8-yl-thiophen-2-yl or 5-(benzo[b]thiophen-2-yl)-thiophen-2-yl is particularly preferred for Het<sup>1</sup>.

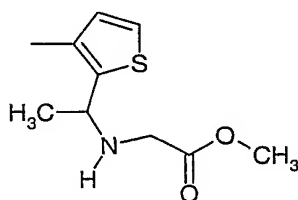
25

Het<sup>2</sup> is a unsaturated mono- or bicyclic heterocyclic radical having 5 to 10 ring members, where 1 or 2 N and/or 1 or 2 S or O atoms can be present and the heterocyclic radical can be mono- or disubstituted by A, Hal, OH, OA, CF<sub>3</sub>, OCF<sub>3</sub>, N(R<sup>5</sup>)<sub>2</sub>, -(CH<sub>2</sub>)<sub>p</sub>-(CHA)<sub>p</sub>-N(R<sup>5</sup>)-(CH<sub>2</sub>)<sub>q</sub>-COR<sup>5</sup>, CHO, COA or COOR<sup>5</sup>.

30

Thiophen-2-yl, 2-formyl-thiophen-3-yl, pyridin-3-yl, pyridin-2-yl, pyridin-4-yl, indol-5-yl, quinolin-8-yl, 4,6-dimethoxy-pyrimidin-2-yl, benzo[b]thiophen-2-yl or

5



is particularly preferred for Het<sup>2</sup>.

10

Het<sup>3</sup> is a partially or completely unsaturated mono- or bicyclic heterocyclic radical having 5 to 10 ring members, where 1 or 2 N atoms are present and the heterocyclic radical can be mono- or disubstituted by A, Hal, OH, OA, CF<sub>3</sub>, OCF<sub>3</sub>, N(R<sup>5</sup>)<sub>2</sub>, SO<sub>2</sub>A or COOR<sup>5</sup> provided that the heterocyclic radical is not bonded via an N atom.

15

Quinolin-5-yl and 1-methanesulfonyl-2,3-dihydro-1H-indol-5-yl is particularly preferred for Het<sup>3</sup>.

20

(CH<sub>2</sub>)<sub>o</sub>-Het is preferentially thiophen-2-yl-ethyl, tetrahydro-furan-2-yl-methyl, 1-methyl-octahydro-indol-3-yl-methyl, 1-methyl-octahydro-indol-3-yl-ethyl, benzo[1,3]dioxol-5-yl-methyl, benzo[1,3]dioxol-5-yl-ethyl, piperazin-1-yl-ethyl, 4-methyl-piperazin-1-yl-propyl, piperidin-1-yl-ethyl, piperidin-4-yl-methyl, 1-methyl-piperidin-3-yl-ethyl, 4-benzyl-piperidin-1-yl-ethyl, 2-methyl-piperidin-1-yl-propyl, 1-ethyl-pyrrolidin-2-yl-methyl, 1-methyl-pyrrolidin-2-yl-methyl, 2-oxo-pyrrolidin-1-yl-propyl, pyridin-2-yl-ethyl, pyridin-4-yl-methyl, pyridin-4-yl-ethyl, imidazol-1-yl-propyl, morpholin-4-yl-propyl or morpholin-4-yl-ethyl.

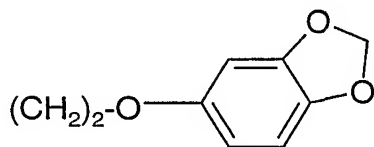
25

(CH<sub>2</sub>)<sub>o</sub>-NR<sup>5</sup>-Het is preferentially (5-nitro-pyridin-2-yl)-amino-ethyl.

30

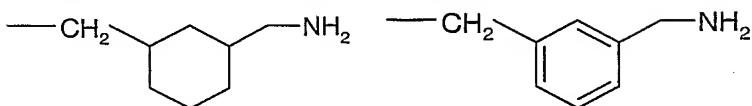
(CH<sub>2</sub>)<sub>o</sub>-OR<sup>5</sup> is preferentially (CH<sub>2</sub>)<sub>2</sub>-OCH<sub>3</sub>, (CH<sub>2</sub>)<sub>3</sub>-OCH<sub>3</sub> or (CH<sub>2</sub>)<sub>3</sub>-O(iPr).

$(\text{CH}_2)_o\text{-OR}^6$  is preferentially

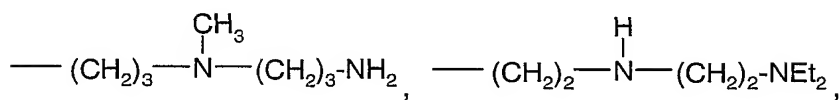
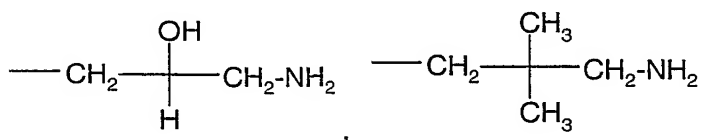


5

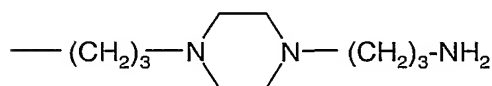
$(\text{CH}_2)_o\text{-Z-(CH}_2)_q\text{-N(R}^5)_2$  is preferentially



10



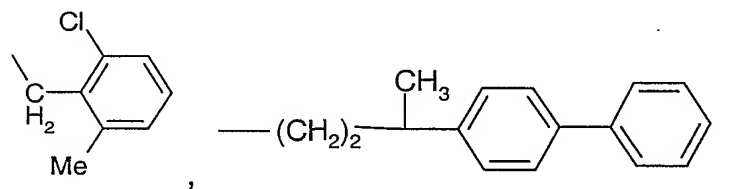
15



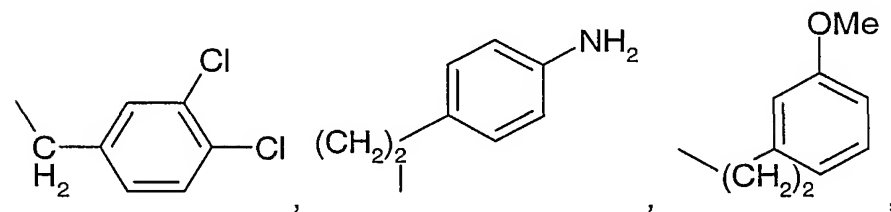
or  $-(\text{CH}_2)_3\text{-O-(CH}_2)_3\text{-NH}_2$ .

$(\text{CH}_2)_p\text{-(CHA)}_p\text{-(CH}_2)_m\text{-Ar}$  is preferentially phenyl,

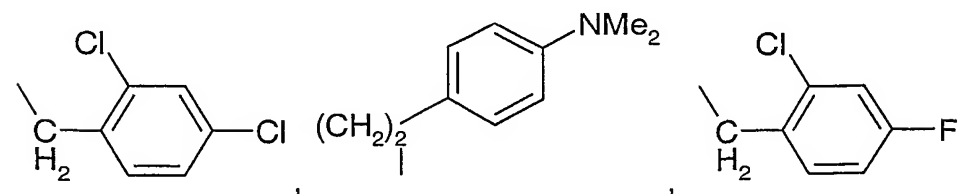
20

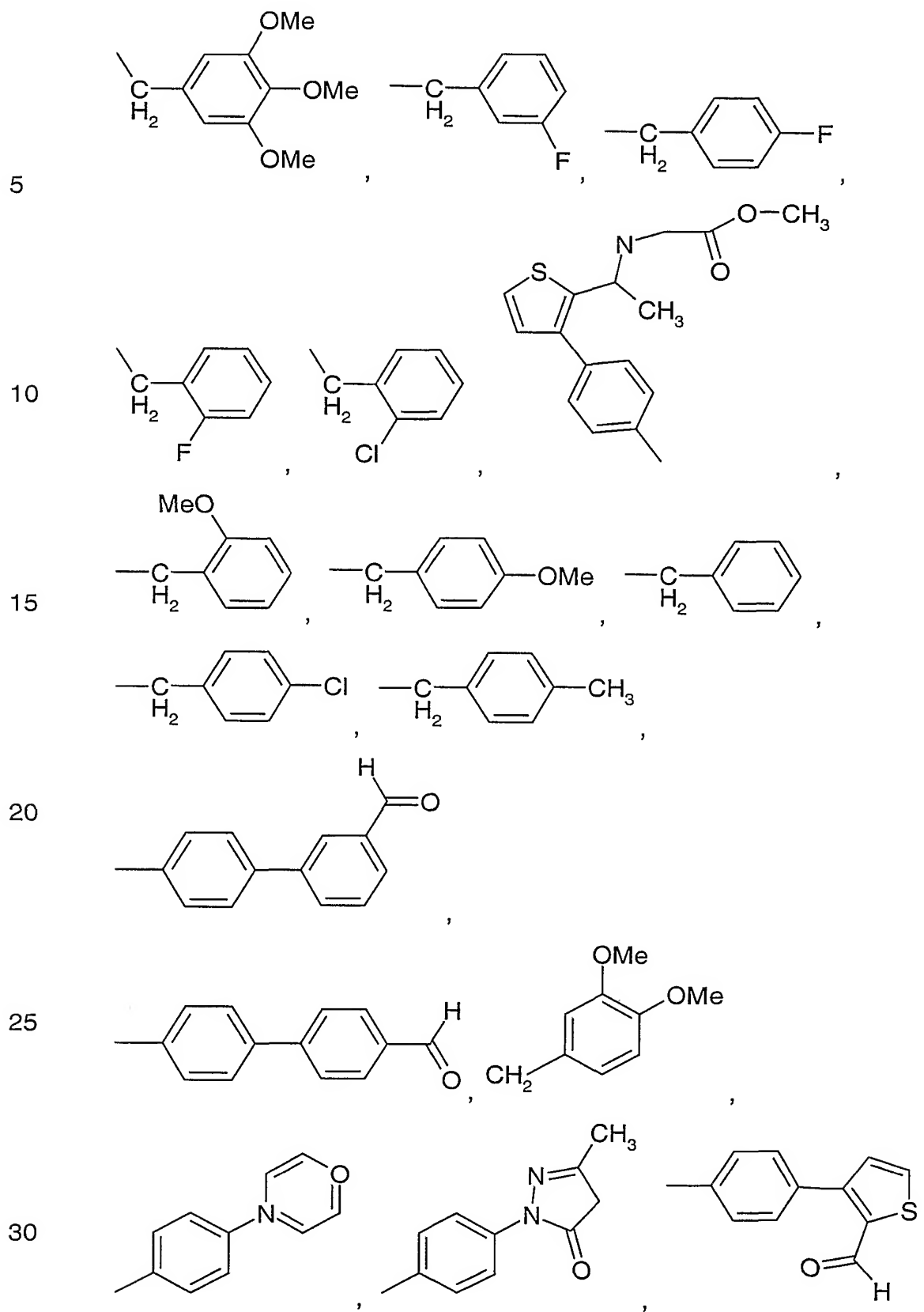


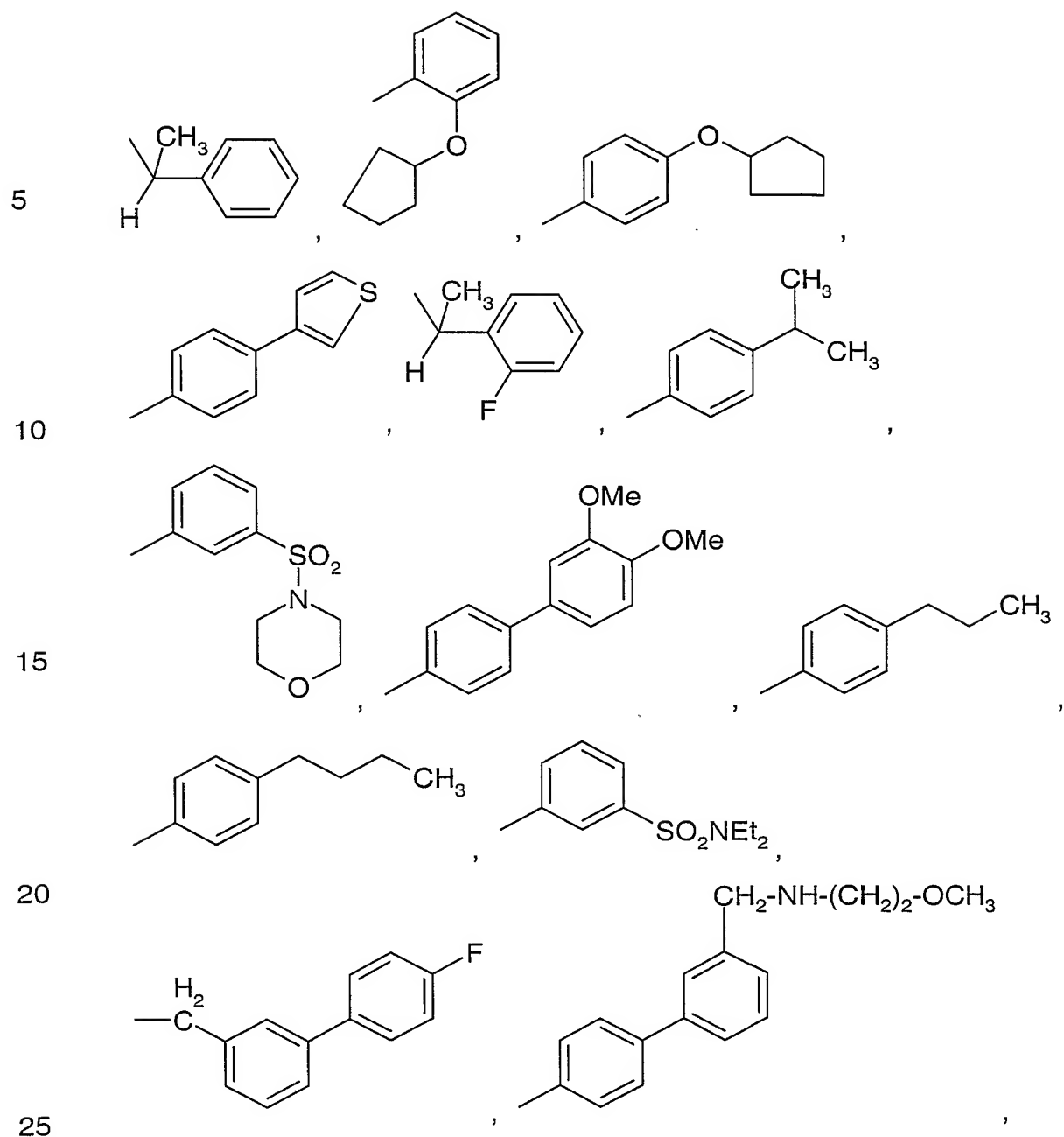
25

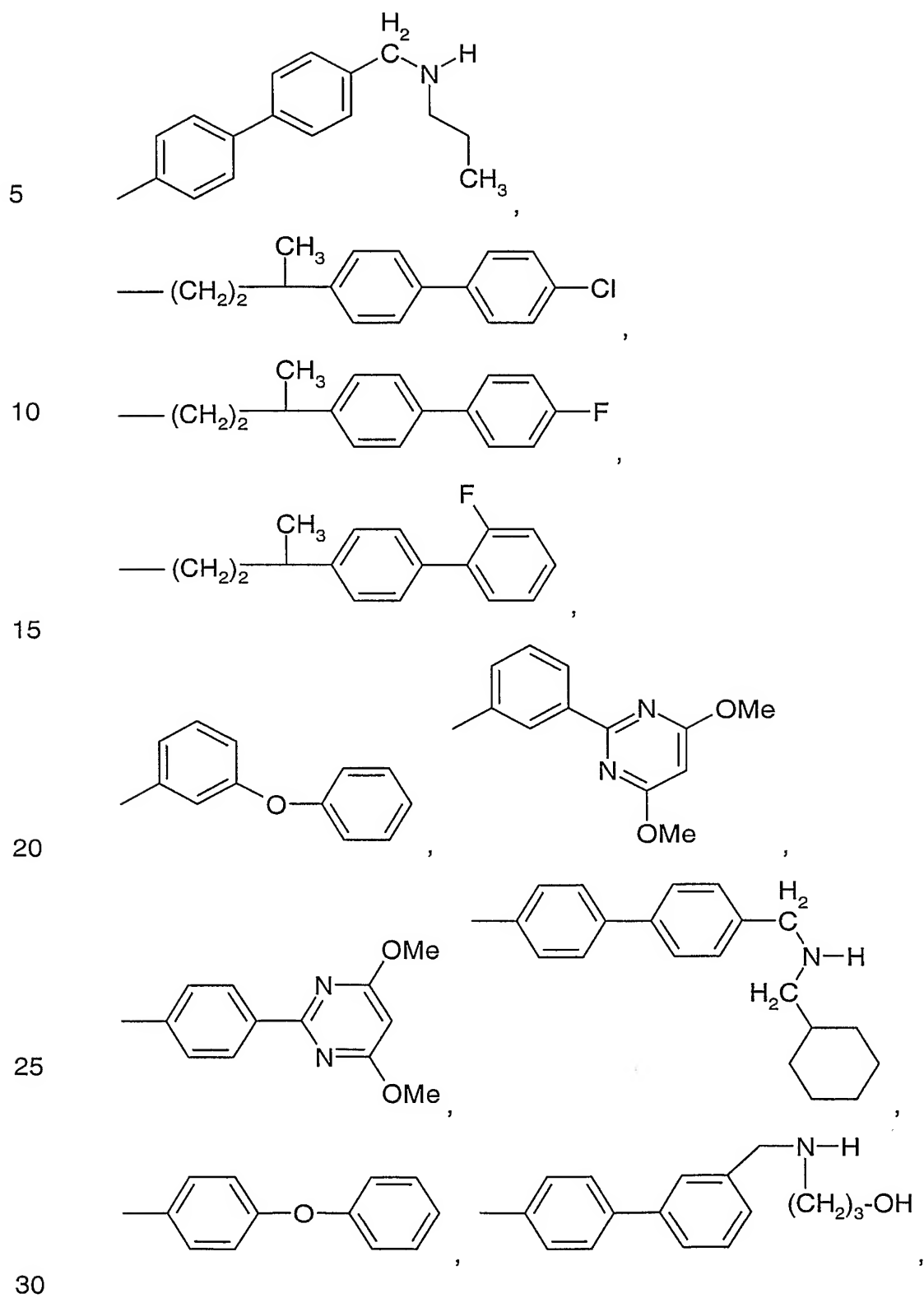


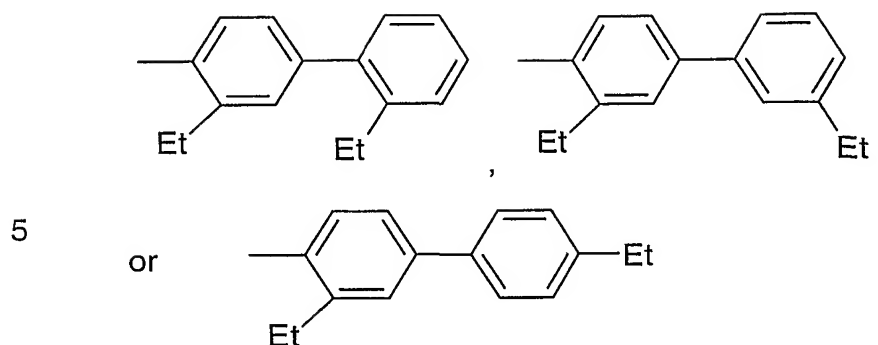
30











10 R and R<sup>1</sup> are independently of each other H, A, OH, OA, Hal, N(R<sup>5</sup>)<sub>2</sub>, NO<sub>2</sub>, CN, CHO, COA, CON(R<sup>5</sup>)<sub>2</sub>, COOR<sup>5</sup>, allyl, CH=CH-COOR<sup>5</sup>,

CH=CHCON(R<sup>5</sup>)<sub>2</sub>, SO<sub>2</sub>A or phenyl, which is unsubstituted or mono-, di- or trisubstituted by A, where A and Hal have a preferred meaning indicated beforehand and R<sup>5</sup> have a preferred meaning indicated in the following.

R is preferentially H or OA.

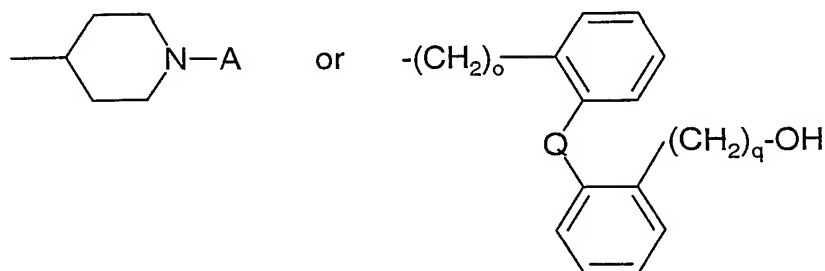
15 R<sup>1</sup> is preferentially H, A, OA, Hal, allyl, CH=CH-COOR<sup>5</sup>, CH=CHCON(R<sup>5</sup>)<sub>2</sub> or phenyl, which is unsubstituted or monosubstituted by A. H, A, OA or Cl is particularly preferred for R<sup>1</sup>.

The preferred position of R<sup>1</sup> is the 6- or 7-position of the quinazoline ring system.

20

R<sup>2</sup> and R<sup>3</sup> are independently of each other H, A, cycloalkyl, -Het<sup>3</sup>, -(CH<sub>2</sub>)<sub>o</sub>-OR<sup>5</sup>, -(CH<sub>2</sub>)<sub>o</sub>-OR<sup>6</sup>, -(CH<sub>2</sub>)<sub>o</sub>-Het, -(CH<sub>2</sub>)<sub>o</sub>-NR<sup>5</sup>-Het, -(CHA)<sub>p</sub>-(CH<sub>2</sub>)<sub>o</sub>-N(R<sup>5</sup>)<sub>2</sub>, -(CH<sub>2</sub>)<sub>p</sub>-(CHA)<sub>p</sub>-(CH<sub>2</sub>)<sub>m</sub>-Ar, -(CH<sub>2</sub>)<sub>o</sub>-Z-(CH<sub>2</sub>)<sub>q</sub>-N(R<sup>5</sup>)<sub>2</sub>,

25



30

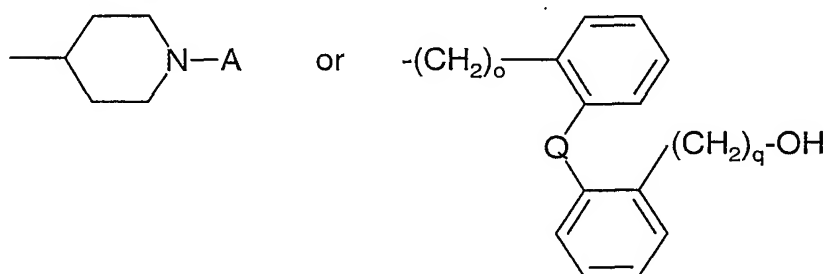
provided that  $R^2$  and  $R^3$  together are not H, where A, Ar, cycloalkyl, Het or Het<sup>3</sup> have a preferred meaning indicated beforehand and  $R^5$ ,  $R^6$ , Q, Z, m, o, p and q have a preferred meaning indicated in the following.

$R^2$  is preferentially H or A.

5

$R^3$  is preferentially A, cycloalkyl, -Het<sup>3</sup>,  $-(CH_2)_o-OR^5$ ,  $-(CH_2)_o-OR^6$ ,  $-(CH_2)_o-Het$ ,  $-(CH_2)_o-NR^5-Het$ ,  $-(CHA)_p-(CH_2)_o-N(R^5)_2$ ,  $-(CH_2)_p-(CHA)_p-(CH_2)_m-Ar$ ,  $-(CH_2)_o-Z-(CH_2)_q-N(R^5)_2$ ,

10



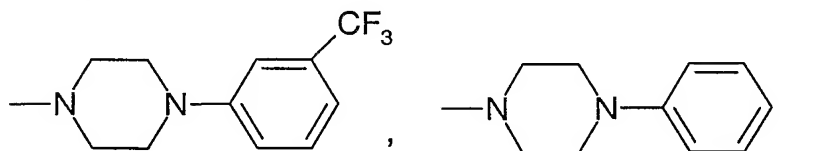
15

Furthermore  $NR^2R^3$  together form a saturated monocyclic heterocyclic radical having 5 to 6 ring members, where 1 or 2 N atoms are present and the heterocyclic radical can be mono- or disubstituted by OH, Ar, OAr or arylalkyl, where Ar or arylalkyl have a preferred meaning indicated beforehand.

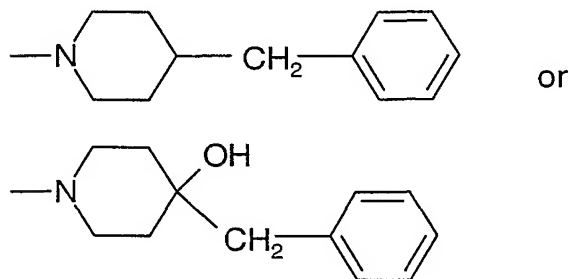
20

Preferred saturated monocyclic heterocyclic radicals can be piperidine or piperazine.

25



30



are particularly preferred for  $\text{NR}^2\text{R}^3$ .

$\text{R}^4$  is Ar or Het<sup>1</sup>, where Ar or Het<sup>1</sup> have a preferred meaning indicated beforehand. Phenyl, 4-bromophenyl, 3,5-bis-(trifluoromethyl)phenyl, 4-tert.-butylphenyl, 3-bromo-6-fluorophenyl, 4-(pyridin-3-yl)phenyl, 3-(pyridin-3-yl)phenyl, 4-(thiophen-2-yl)phenyl, 3-(thiophen-2-yl)phenyl, naphthyl, biphenyl-4-yl, 4'-fluorobiphenyl-4-yl, 4'-fluorobiphenyl-3-yl, 4'-chlorobiphenyl-4-yl, 4'-chlorobiphenyl-3-yl, 4'-methoxybiphenyl-4-yl, 4'-methoxybiphenyl-3-yl, (3',5'-dichloro)biphenyl-3-yl is particularly preferred as Ar in  $\text{R}^4$ .

Phenyl, 4-bromophenyl, 3,5-bis-(trifluoromethyl)phenyl, 4-tert.-butylphenyl, 3-bromo-6-fluorophenyl, 4-(pyridin-3-yl)phenyl, 3-(pyridin-3-yl)phenyl, 4-(thiophen-2-yl)phenyl, 3-(thiophen-2-yl)phenyl, naphthyl, biphenyl-4-yl, 4'-fluorobiphenyl-4-yl, 4'-fluorobiphenyl-3-yl, 4'-chlorobiphenyl-4-yl, 4'-chlorobiphenyl-3-yl, 4'-methoxybiphenyl-4-yl, 4'-methoxybiphenyl-3-yl, (3',5'-dichloro)biphenyl-3-yl, 5-(4-fluorophenyl)-thiophen-2-yl, 5-(2-methoxyphenyl)-thiophen-2-yl, 5-(2-cyanophenyl)-thiophen-2-yl, 5-(2,5-dimethoxyphenyl)-thiophen-2-yl, 2-[2,2']bithiophenyl-5-yl, 5-(pyridin-4-yl)-thiophen-2-yl, 5-(1H-indol-5-yl)-thiophen-2-yl, 5-quinolin-8-yl-thiophen-2-yl or 5-(benzo[b]thiophen-2-yl)-thiophen-2-yl is particularly preferred for  $\text{R}^4$ .

$\text{R}^5$  is H or A, where A has a preferred meaning indicated beforehand.

$\text{R}^6$  is benzo[1,3]dioxol-5-yl.

$\text{R}^7$  is H, A, cycloalkyl or  $(\text{CH}_2)_q\text{-OR}^5$ , where A, cycloalkyl and  $\text{R}^5$  have a preferred meaning indicated beforehand and q is preferably 2 or 3.

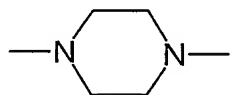
Q is O or S, preferentially O.

Y is a direct bond,  $(\text{CH}_2)_n$  or  $\text{-NR}^5\text{-(CH}_2)_m\text{-}$ , where  $\text{R}^5$  has a preferred meaning indicated beforehand and n and m have a preferred meaning

indicated in the following. Y is preferentially a direct bond or  $(CH_2)_n$ , very particularly preferably a direct bond.

Z is phenylene, cyclohexylene,  $-NR^5-$ , O,  $-CH(OH)-$ ,  $-CA_2-$  or

5



, where  $R^5$  and A have a preferred meaning indicated beforehand. Phenylene and/or cyclohexylene are particularly bonded in 1,4- or 1,3-position.

10

n is 1, 2, 3, 4, 5 or 6, preferentially 4.

m is 0, 1, 2, 3, 4, 5 or 6, preferentially 0, 1, 2 or 3.

o is 1, 2, 3, 4, 5, 6 or 7, preferentially 1, 2, 3 or 7.

p is 0, 1, 2, 3 or 4, preferentially 0, 1 or 2.

15

q is 1, 2, 3 or 4, preferentially 1, 2 or 3.

Some preferred groups of compounds can be expressed by the following subformulae Ia to In, which correspond to the formula I and in which the radicals not designated in greater detail have the meanings indicated in formula I, but in which

20

in Ia    R    is H or OA and  
            $R^1$     is H, A, OA or Hal;

25

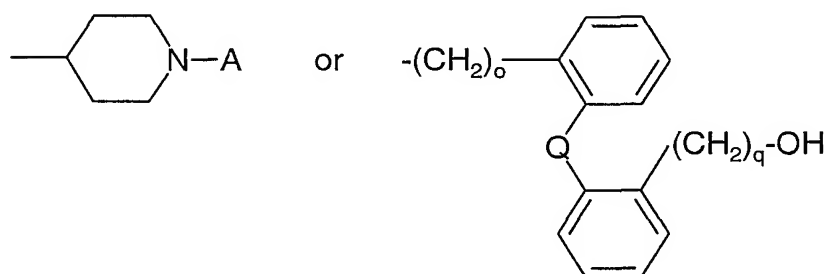
in Ib    R    is H or OA,  
            $R^1$     is H, A, OA or Hal and  
           Y    is  $(CH_2)_n$ ;

30

in Ic    R    is H or OA,  
            $R^1$     is H, A, OA or Hal,  
            $R^4$     is Ar,  
           Ar    is unsubstituted phenyl and

- Y is  $(\text{CH}_2)_n$ ;
- 5 in Id R is H or OA,  
 $\text{R}^1$  is H, A, OA or Hal and  
Y is a direct bond;
- 10 in le R is H or OA,  
 $\text{R}^1$  is H, A, OA or Hal and  
Y is  $-\text{N}(\text{R}^5)-(\text{CH}_2)_m-$ ;
- 15 in lf R is H or OA,  
 $\text{R}^1$  is H, A, OA or Hal,  
 $\text{R}^4$  is Ar and  
Y is a direct bond;
- 20 in lg R is H or OA,  
 $\text{R}^1$  is H, A, OA or Hal,  
 $\text{R}^4$  Ar,  
Ar is phenyl or biphenyl, which is unsubstituted or substituted by  
Hal, Het<sup>2</sup>, OA or  $-(\text{CH}_2)_p-\text{N}(\text{R}^7)_2$ ,  
 $\text{R}^7$  is H, A, cycloalkyl,  $(\text{CH}_2)_3-\text{OR}^5$  or  $(\text{CH}_2)_2-\text{OR}^5$  and  
Y is a direct bond;
- 25 in lh R is H,  
 $\text{R}^1$  is Hal,  
 $\text{R}^2$  is H,  
 $\text{R}^3$  is  $-(\text{CH}_2)_o-\text{Het}$ ,  $-(\text{CHA})_p-(\text{CH}_2)_o-\text{N}(\text{R}^5)_2$  or  
 $-(\text{CH}_2)_p-(\text{CHA})_p-(\text{CH}_2)_m-\text{Ar}$ ,  
 $\text{R}^4$  is Ar
- 30 Ar is unsubstituted phenyl and  
Y is a direct bond;

- in li R is H,  
 $R^1$  is Hal,  
 $R^2$  is H,  
 $R^3$  is  $-(CH_2)_o-Het$ ,  $-(CHA)_p-(CH_2)_o-N(R^5)_2$ ,  $-(CH_2)_o-NR^5-Het$ ,  
 5  $-(CH_2)_o-Z-(CH_2)_q-N(R^5)_2$  or  $-(CH_2)_p-(CHA)_p-(CH_2)_m-Ar$ ,  
 $R^4$  is Ar,  
 Ar is biphenyl-4-yl and  
 Y is a direct bond;
- 10 in lj R is H,  
 $R^1$  is Hal,  
 $R^2$  is H or A,  
 $R^3$  is A, cycloalkyl,  $-Het^3$ ,  $-(CH_2)_o-OR^5$ ,  $-(CH_2)_o-OR^6$ ,  $-(CH_2)_o-Het$ ,  
 15  $-(CH_2)_o-NR^5-Het$ ,  $-(CHA)_p-(CH_2)_o-N(R^5)_2$ ,  $-(CH_2)_p-(CHA)_p-(CH_2)_m-Ar$ ,  $-(CH_2)_o-Z-(CH_2)_q-N(R^5)_2$ ,



20

25

or  $NR^2R^3$  together form a saturated monocyclic heterocyclic radical having 5 to 6 ring members, where 1 or 2 N atoms are present and the heterocyclic radical can be mono- or disubstituted by OH, Ar, OAr or arylalkyl,

$R^4$  is Ar,  
 Ar is phenyl which is substituted by Br and  
 Y is a direct bond;

30

- in lk R is H,  
 $R^1$  is Hal,  
 $R^2$  is H,

$R^3$  is  $-(CH_2)_o$ -Het or  $-(CHA)_p$ -( $CH_2$ )<sub>o</sub>-N( $R^5$ )<sub>2</sub>,  
 $R^4$  is Ar,  
 Ar is phenyl or biphenyl, which is unsubstituted or substituted by  
 Hal, Het<sup>2</sup>, OA or  $-(CH_2)_p$ -N( $R^7$ )<sub>2</sub>,  
 5  $R^7$  is H, A, cycloalkyl,  $(CH_2)_3$ -OR<sup>5</sup> or  $(CH_2)_2$ -OR<sup>5</sup> and  
 Y is a direct bond;

in Im  $R$  is H,  
 $R^1$  is Hal,  
 10  $R^2$  is H,  
 $R^3$  is  $-(CH_2)_o$ -Het or  $-(CHA)_p$ -( $CH_2$ )<sub>o</sub>-N( $R^5$ )<sub>2</sub>,  
 $R^4$  is Het<sup>1</sup>,  
 Het<sup>1</sup> is thiophen-2-yl, which is substituted by Ar or Het<sup>2</sup>,  
 $R^7$  is H, A, cycloalkyl,  $(CH_2)_3$ -OR<sup>5</sup> or  $(CH_2)_2$ -OR<sup>5</sup> and  
 15 Y is a direct bond;

in In  $R$  is H,  
 $R^1$  is Hal,  
 $R^2$  is H,  
 20  $R^3$  is  $-(CH_2)_o$ -Het or  $-(CHA)_p$ -( $CH_2$ )<sub>o</sub>-N( $R^5$ )<sub>2</sub>,  
 $R^4$  is Het<sup>1</sup>,  
 Het<sup>1</sup> is 5-(4-fluoro-phenyl)-thiophen-2-yl, 5-(2-methoxy-phenyl)-  
 thiophen-2-yl, 5-(2-cyano-phenyl)-thiophen-2-yl, 5-(2,5-  
 dimethoxy-phenyl)-thiophen-2-yl, 2-[2,2']bithiophenyl-5-yl, 5-  
 25 (1H-indol-5-yl)-thiophen-2-yl, 5-pyridine-4-yl-thiophen-2-yl, 5-  
 quinolin-8-yl-thiophen-2-yl or 5-benzo[b]thiophen-2-yl-  
 thiophen-2-yl  
 $R^7$  is H, A, cycloalkyl,  $(CH_2)_3$ -OR<sup>5</sup> or  $(CH_2)_2$ -OR<sup>5</sup> and  
 Y is a direct bond.

30

The compounds of the formula I and also the starting substances for their preparation are otherwise prepared by methods known per se, such as are

described in the literature (e.g. in the standard works such as Houben-Weyl, Methoden der organischen Chemie [Methods of Organic Chemistry], Georg-Thieme-Verlag, Stuttgart), namely under reaction conditions which are known and suitable for the reactions mentioned. In this case, use can also be made of variants which are known per se, but not mentioned here in greater detail.

The starting substances, if desired, can also be formed in situ such that they are not isolated from the reaction mixture, but immediately reacted further to give the compounds of the formula I.

The compounds of the formula I can be obtained by liberating them from their functional derivatives by solvolysis, in particular hydrolysis or by hydrogenolysis.

Preferred starting substances for the solvolysis or hydrogenolysis are those which otherwise correspond to the formula I, but instead of one or more free amino and/or hydroxyl groups contain corresponding protected amino and/or hydroxyl groups, in particular those which instead of an H-N- group carry an R'-N- group, in which R' is an amino protective group and/or those which instead of the H atom of a hydroxyl group carry a hydroxyl protective group, e.g. those which correspond to the formula I, but instead of a group -COOH carry a group -COOR", in which R" is a hydroxyl protective group.

A number of - identical or different - protected amino and/or hydroxyl groups can also be present in the molecule of the starting substance. If the protective groups present are different from one another, in many cases they can be removed selectively (lit.: T.W. Greene, P.G.M. Wuts, *Protective Groups in Organic Chemistry*, 2nd ed., Wiley, New York 1991 or P.J. Kocienski, *Protecting Groups*, 1st ed., Georg Thieme Verlag, Stuttgart - New-York, 1994).

The expression "amino protective group" is generally known and relates to groups which are suitable for protecting (for blocking) an amino group against chemical reactions, but which are easily removable after the desired chemical reaction has been carried out at other positions in the molecule. Typical groups of this type are, in particular, unsubstituted or substituted acyl, aryl, aralkoxymethyl or aralkyl groups. Since the amino protective groups are removed after the desired reaction (or reaction sequence), their nature and size is otherwise not critical; however, those having 1-20, in particular 1-8, C atoms are preferred. The expression "acyl group" is to be interpreted in the widest sense in connection with the present process. It includes acyl groups derived from aliphatic, araliphatic, aromatic or heterocyclic carboxylic acids or sulfonic acids and, in particular, alkoxycarbonyl groups, aryloxycarbonyl groups and especially aralkoxycarbonyl groups. Examples of acyl groups of this type are alkanoyl such as acetyl, propionyl, butyryl; aralkanoyl such as phenylacetyl; aroyl such as benzoyl or toluyl; aryloxyalkanoyl such as POA; alkoxycarbonyl such as methoxycarbonyl, ethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, BOC, 2-iodoethoxycarbonyl; aralkyloxycarbonyl such as CBZ ("carbobenzoxyl"), 4-methoxybenzyloxycarbonyl (MOZ), 4-Nitro-benzyloxycarbonyl oder 9-fluorenylmethoxycarbonyl (Fmoc); 2-(phenylsulfonyl)ethoxycarbonyl; trimethylsilylethoxycarbonyl (Teoc) or arylsulfonyl such as 4-methoxy-2,3,6-trimethylphenyl-sulfonyl (Mtr). Preferred amino protective groups are BOC, furthermore CBZ, Fmoc, benzyl and acetyl; particularly preferred Fmoc.

25

The expression "hydroxyl protective group" is also generally known and relates to groups which are suitable for protecting a hydroxyl group against chemical reactions, but which are easily removable after the desired chemical reaction has been carried out at other positions in the molecule.

30

Typical groups of this type are the above mentioned unsubstituted or substituted aryl, aralkyl, aroyl or acyl groups, furthermore also alkyl groups,

alkyl-, aryl- or aralkylsilyl groups or O,O- or O,S-acetals. The nature and size of the hydroxyl protective groups is not critical, since they are removed again after the desired chemical reaction or reaction sequence; groups having 1-20, in particular 1-10 C atoms, are preferred. Examples of

5 hydroxyl protective groups are, inter alia, benzyl, 4-methoxybenzyl or 2,4-dimethoxybenzyl, aroyl groups such as benzoyl or p-nitrobenzoyl, acyl groups such as acetyl or pivaloyl, p-toluolsulfonyl, alkyl groups such as methyl or tert-butyl, but also allyl, alkylsilyl groups such as trimethylsilyl (TMS), triisopropylsilyl (TIPS), tert-butyldimethylsilyl (TBS) or triethylsilyl,

10 trimethylsilylethyl, aralkylsilyl groups such as tert-butyldiphenylsilyl (TBDPS), cyclic acetals such as isopropylidene-, cyclopentylidene-, cyclohexylidene-, benzylidene-, p-methoxybenzylidene- or o,p-dimethoxybenzylideneacetal, acyclic acetals such as tetrahydropyranyl (Thp), methoxymethyl (MOM), methoxyethoxymethyl (MEM),

15 benzyloxymethyl (BOM) or methylthiomethyl (MTM). Acetyl, benzyl, tert-butyl or TBS being particularly preferred.

The liberation of the compounds of the formula I from their functional derivatives depending on the protective group used is known in the present

20 literature such as T.W. Greene, P.G.M. Wuts, *Protective Groups in Organic Chemistry*, 2nd ed., Wiley, New York 1991, P.J. Kocienski, *Protecting Groups*, 1st ed., Georg Thieme Verlag, Stuttgart - New-York, 1994. In this case, use can also be made of variants which are known per se, but not mentioned here in greater detail.

25 The groups BOC and O-tert-butyl can preferably be removed, for example, using TFA in dichloromethane or using approximately 3 to 5N HCl in dioxane at 15-30°C, the Fmoc group using an approximately 5 to 50% solution of dimethylamine, diethylamine or piperidine in DMF at 15-30°C.

30 Preferred starting substances for the solvolysis or hydrogenolysis includes also those which otherwise correspond to the formula I, but are attached to

a solid phase. The liberation of the compounds of the formula I from the solid phase is known in the present literature such as Novabiochem - The Combinatorial Chemistry Catalog, March 99 and cited literature.

- 5       The solid phase with a carbonate moiety as terminal functional group can preferably be removed, for example, using TFA (50%) in dichloromethane.

The quinazolines of formula I can also preferably be prepared, using either solution or solid-phase techniques.

10

The term solid phase indicates a resin for solid-phase chemistry, especially for combinatorial chemistry, i.e. by robot- and computer-assisted syntheses, and subjected to mass screening as indicated in US 5,463,564; M. A. Gallop et al., J. Med. Chem. 1994, 37, 1233-1251 and 1385-1401 and M.J. Sofia, Drug Discovery Today 1996, 1, 27-34). The polymeric material of the solid phase is generally chosen from the group consisting of cross-linked polystyrene, cross-linked polyacrylamide or other resins, natural polymers or silicagels.

15

- 20       The group of cross-linked polystyrene, cross-linked polyacrylamide or other resins includes e.g. polyacrylamide, polymethacrylamide, polyhydroxyethylmethacrylate, polyamide, polystyrene, (meth)acrylate copolymers, for instance from (meth)acrylic acid, esters of (meth)acrylic acid and/or 2-methylene-succinic acid, but-2-enoic acid or maleic acid, 25       polyurethanes or other copolymers.

Suitable terminal functional groups or linkers on the surface of the resin have to be chosen to attach the compounds to the resin. There exists a variety of commercially available resins, e.g. in Novabiochem - The

30

Combinatorial Chemistry Catalog, March 99. Examples for suitable resins are carbonate resins with a modified carbonate group as terminal functional group like p-nitrophenylcarbonate resin, halogenated resins like Merrifield

resin (chloromethylpolystyrene) or carboxy resins like carboxy polystyrene resin or NovaSyn<sup>®</sup> TG Carboxy Resin. p-Nitrophenylcarbonate resin is particularly preferred. These and other types of resins well known in the art can be used in the subject invention.

5

The quinazolines of formula I, in which Y is a direct bond or  $(CH_2)_n$ , can preferably be prepared by combining and reacting a 2-amino-benzonitrile of formula II with an aldehyde of formula III followed by converting the cyano group to an amide group, reacting the given formula IV with a base, chlorinating the given quinazolin-4-one of formula V and reacting the given formula VI with an amine of formula VII. The conversion of the cyano group to the amide group occurs by conventional means which are known to a skilled artisan. Particularly, the conversion occurs via oxidation within the presence of a base.

10

15

The quinazolines of formula I, in which Y is  $-N(R^5)-(CH_2)_m-$ , can be prepared by reacting a 2,4-dichloro-quinazoline of formula VIII with an amine of formula VII and reacting the given formula IX with an amine of formula X.

20

As a rule, the starting compounds of the formulae II, III, VII, VIII and X are known or commercially available.

The unknown compounds, however, can be prepared by methods known per se.

25

The 2,4-dichloro-quinazolines of formula II in which R and  $R^1$  have a meaning indicated in claim 1 can be prepared by reacting a substituted anthranilic acid with KOCN/acetic acid in the presence of a base and chlorinating the given 1H-quinazoline-2,4-dione.

30

The aldehydes of formula III, as a rule, are also commercially available. Furthermore, syntheses for the preparation of aldehydes of formula III, such as, for example, the oxidation of an alcohol, can be used.

- 5 The amines of formula VII or X in which  $R^2$ ,  $R^3$ ,  $NR^2R^3$ ,  $R^5$ ,  $R^4$  and  $m$  have a meaning indicated in claim 1, as a rule, are also commercially available and can be attached to the suitable resin or to a compound of formula VI, VIII or IX by coupling procedures well known in the art and as described in the ensuing Examples. Furthermore, syntheses for the preparation of
- 10 amines of formula VII or X, such as, for example, the Gabriel synthesis, can be used.

- For the preparation of compounds of the formula I in which  $R^4$  is unsubstituted or substituted biphenyl, heteroarylsubstituted phenyl or aryl-
- 15 or heteroaryl-substituted thiophenyl, an appropriate compound of the formula I in which  $R^4$  is phenyl chloride, phenyl bromide, phenyl iodide, thiophenyl chloride, thiophenyl bromide or thiophenyl iodide can be reacted with the appropriate boronic acid derivatives in a Suzuki type coupling reaction. This reaction is expediently carried out under Palladium catalysis
- 20 with different phosphines as coordination ligands, e.g.  $Pd(P(Ph)_3)_2$ ,  $Pd(II)Cl_2dppf$ ,  $PdOAc_2 + P(R^*)_3$  ( $R^* =$  phenyl, cyclohexyl, tert-butyl) etc. in the presence of a base such as potassium carbonate, cesium carbonate, DBU, NaOH, in an inert solvent or solvent mixture, e.g. DMF or 1,4-dioxane at temperatures between  $0^\circ$  and  $150^\circ$ , preferably between  $60^\circ$  and  $120^\circ$ .
- 25 Depending on the conditions used, the reaction time is between a few minutes and a number of days. The boronic acid derivatives can be prepared by conventional methods or are commercially available. The reactions can be carried out in analogy to the methods indicated in Suzuki et al., J. Am. Chem. Soc. 1989, 111, 314ff., Suzuki et al., Chem. Rev.
- 30 1995, 95, 2457ff and G.C. Fu et al. Angew. Chem 1998, 110, 3586. The Suzuki type coupling reaction can be furthermore used to convert radicals  $R$  and  $R^1$  into other radicals  $R$  and  $R^1$ , for e.g. to convert a halogen

substituted quinazolines to a quinazoline substituted by substituted or unsubstituted phenyl.

5 For the preparation of compounds of the formula I in which R or R<sup>1</sup> is allyl, an appropriate compound of the formula I in which R<sup>4</sup> is quinazoline chloride, quinazoline bromide or quinazoline iodide can be reacted with allyltributyltin in a Stille type coupling reaction. This reaction is expediently carried out under Palladium catalysis with different phosphines as coordination ligands, e.g. Pd(P(Ph)<sub>3</sub>)<sub>2</sub>, Pd(II)Cl<sub>2</sub>dppf, PdOAc<sub>2</sub> + P(R\*)<sub>3</sub> (R\* = phenyl, cyclohexyl, tert-butyl) etc. in an inert solvent or solvent mixture, 10 e.g. DMF or 1,4-dioxane at temperatures between 0° and 150°, preferably between 60° and 120°. Depending on the conditions used, the reaction time is between a few minutes and a number of days.

15 For the preparation of compounds of the formula I in which R or R<sup>1</sup> is CH=CH-COOR<sup>5</sup> or CH=CH-CON(R<sup>5</sup>)<sub>2</sub>, an appropriate compound of the formula I in which R<sup>4</sup> is quinazoline chloride, quinazoline bromide or quinazoline iodide can be reacted with substituted acrylate in a Heck type coupling reaction. This reaction is expediently carried out under Palladium catalysis with different phosphines as coordination ligands, e.g. 20 Pd(P(Ph)<sub>3</sub>)<sub>2</sub>, Pd(II)Cl<sub>2</sub>dppf, PdOAc<sub>2</sub> + P(R\*)<sub>3</sub> (R\* = phenyl, cyclohexyl, tert-butyl) etc. in the presence of a base such as triethyl amine or a catalyst tetrabutylammonium iodide, in an inert solvent or solvent mixture, e.g. DMF or 1,4-dioxane at temperatures between 0° and 150°, preferably between 25 60° and 120°. Depending on the conditions used, the reaction time is between a few minutes and a number of days.

A base of the formula I can be converted into the associated acid addition salt using an acid, for example by reaction of equivalent amounts of the 30 base and of the acid in an inert solvent such as ethanol and subsequent evaporation. Acids which give physiologically acceptable salts are

particularly suitable for this reaction. Thus inorganic acids can be used, e.g. sulfuric acid, nitric acid, hydrohalic acids such as hydrochloric acid or hydrobromic acid, phosphoric acids such as orthophosphoric acid, sulfamic acid, furthermore organic acids, in particular aliphatic, alicyclic, araliphatic, aromatic or heterocyclic mono- or polybasic carboxylic, sulfonic or sulfuric acids, e.g. formic acid, acetic acid, propionic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, lactic acid, tartaric acid, malic acid, citric acid, gluconic acid, ascorbic acid, nicotinic acid, isonicotinic acid, methane- or ethanesulfonic acid, p-toluenesulfonic acid, naphthalenemono- and disulfonic acids or laurylsulfuric acid. Salts with physiologically unacceptable acids, e.g. picrates, can be used for the isolation and/or purification of the compounds of the formula I.

On the other hand, compounds of the formula I with bases (e.g. sodium or potassium hydroxide or carbonate) can be converted into the corresponding metal salts, in particular alkali metal or alkaline earth metal salts, or into the corresponding ammonium salts.

The invention furthermore relates to pharmaceutical preparations comprising at least one compound of the formula I and/or one of its physiologically acceptable salts, which are prepared, in particular, in a non-chemical way. In this case, the compounds of the formula I according to the invention can be brought into a suitable dose form together with at least one solid, liquid and/or semi-liquid excipient or auxiliary and, if appropriate, in combination with one or more other active compounds.

These preparations can be used as medicaments in human or veterinary medicine. Possible excipients are organic or inorganic substances which are suitable for enteral (e.g. oral) or parenteral administration or topical application and do not react with the novel compounds, for example water, vegetable oils, benzyl alcohols, alkylene glycols, polyethylene glycols, glyceryl triacetate, gelatin, carbohydrates such as lactose or starch,

magnesium stearate, talc and petroleum jelly. Tablets, pills, coated tablets, capsules, powders, granules, syrups, juices or drops are used, in particular, for oral administration, suppositories are used for rectal administration, solutions, preferably oily or aqueous solutions, furthermore suspensions, emulsions or implants, are used for parenteral administration, and ointments, creams or powders are used for topical application. The novel compounds can also be lyophilized and the lyophilizates obtained used, for example, for the production of injection preparations. The preparations indicated can be sterilized and/or can contain auxiliaries such as lubricants, preservatives, stabilizers and/or wetting agents, emulsifiers, salts for affecting the osmotic pressure, buffer substances, colorants, flavorings and/or one or more other active compounds, e.g. one or more vitamins.

The compounds of the formula I and their physiologically acceptable salts act as adhesion receptor antagonists, in particular glycoprotein IbIX antagonists, and can be employed for the prophylaxis and/or therapy of thrombotic disorders and sequelae deriving therefrom. The disorders are acute coronary syndromes, angina pectoris, myocardial infarct, peripheral circulatory disorders, stroke, transient ischaemic attacks, arteriosclerosis and reocclusion/restenosis after angioplasty/stent implantation.

In this case, the substances according to the invention are as a rule administered in the dose of the glycoprotein IIbIIIa antagonist ReoPro® of preferably between approximately 1 and 500 mg, in particular between 5 and 100 mg, per dose unit. The daily dose is preferably between approximately 0.02 and 10 mg/kg of body weight. The specific dose for each patient depends, however, on all sorts of factors, for example on the efficacy of the specific compound employed, on the age, body weight, general state of health and sex, on the diet, on the time and route of administration, and on the excretion rate, pharmaceutical combination and

severity of the particular disorder to which the therapy applies. Oral administration is preferred.

5 Above and below, all temperatures are indicated in °C. In the following examples, "customary working-up" for solution reactions means: if necessary, water is added, if necessary, depending on the constitution of the final product, the mixture is adjusted to pHs between 2 and 10 and extracted with ethyl acetate or dichloromethane, the organic phase is separated off, dried over sodium sulfate and evaporated, and the residue is  
10 purified by chromatography on silica gel and/or by crystallization.

"Customary working-up" for solid-phase reactions means: the crude reaction is filtered and washed with DMF twice, then successively with methanol and methylene chloride three times, and finally once with methyl  
15 tert-butyl ether. The resin is then dried in vacuo.

Mass spectrometry (MS) apparatuses Kratos OMIT and Finnigan LCQ. (M+H)<sup>+</sup> values or M<sup>+</sup> values are determined.

20

## EXAMPLES

### Example 1:

1. Pyridine (0,144 mole) is given to a solution of 2-amino-4-chlorobenzonitrile (0,131 mole) in 100 ml tetrahydrofuran (THF) and a solution of 4-bromobenzoylchloride (31,6 g, 0,144 mole) in 50 ml THF is  
25 added under nitrogen. After addition of 100 ml THF, the mixture is stirred for 6 h at room temperature (rt). The crude reaction is then customary worked up for solution reactions affording 4-bromo-N-(5-chloro-2-cyano-phenyl)-benzamide as a solid; m.p. 151-152°.

MS calc.: 335,6 ; found: 336, 338.

30

2. A suspension of 4-bromo-N-(5-chloro-2-cyano-phenyl)-benzamide (30 g, 89,4 mmol) in 500 ml methanol is mixed with 130 ml NaOH (2N) and perhydrite tablets [(H<sub>2</sub>O<sub>2</sub>), 50 g]. The mixture is heated to boiling for 2 hrs. After cooling to rt and customary working up 4-bromo-N-(5-chloro-2-aminocarbonyl-phenyl)-benzamide is obtained as a solid; m.p. 172-173°.

5 MS calc.: 354 ; found: 354.

3. 4-Bromo-N-(5-chloro-2-aminocarbonyl-phenyl)-benzamide (18,25 g, 51,6 mmol) is solved in 250 ml dioxane and 250 ml NaOH (1N) are added. The mixture is heated to boiling for 5 days. After cooling to rt and customary working up 2-(4-bromo-phenyl)-7-chloro-3H-quinazolin-4-one is obtained as a solid; m.p. > 300°.

10 MS calc.: 336 ; found: 336.

4. 2-(4-Bromo-phenyl)-7-chloro-3H-quinazolin-4-one (38,7 mmol) is added to 50 ml thionylchloride and is heated at 40°. The mixture is treated with 6 ml dimethylformamide (DMF). After cooling to rt the mixture is stirred for 3 hrs. Customary working up gives 2-(4-bromo-phenyl)-4,7-dichloro-quinazoline as a solid; m.p. 189-190°.

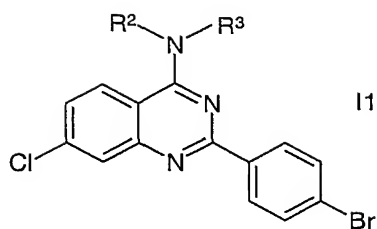
15 MS calc.: 354.0 ; found: 355.

5. A solution of 2-(4-bromo-phenyl)-4,7-dichloro-quinazoline (0,085 mmol, 30 mg) in 2 ml THF is treated with aniline (0,01 ml, 0,11 mmol). The suspension is heated to 60° and stirred for 18 hrs. The reaction mixture is filtered and the crystals are washed with THF and dried. [2-(4-Bromo-phenyl)-7-chloro-quinazolin-4-yl]-phenyl-amine is obtained.

25 MS calc.: 410,7 ; found: 411.

#### Example 2:

30 Analogously to example 1, 1-(4-bromo-phenyl)-4,7-dichloro-quinazoline is reacted with HNR<sup>2</sup>R<sup>3</sup> to obtain compounds of formula I1



5

according to table 1.

Table 1: 4-bromophenyl-quinazolines of formula I1

10

15

20

25

30

R <sup>2</sup> in HNR <sup>2</sup> R <sup>3</sup> and in I1	R <sup>3</sup> in HNR <sup>2</sup> R <sup>3</sup> and in I1	MS calc.	found
H		506,8	507
H		494,8	495
H		494,8	495
H		559,9	560
H		545,9	546
H		548,8	549
H		548,8	550
H		461,8	463

5	H		495,8	496
	H		438,8	439
	H		438,8	439
	H		438,8	439
10	H		452,8	453
	H		452,8	453
	H		466,8	467
15	H		502,8	503
	H		502,8	503
20	H		529,9	530

Example 3:

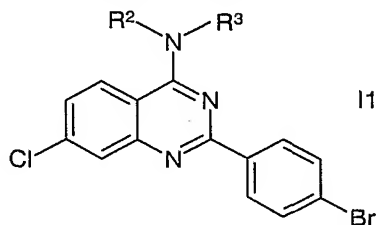
A solution of 2-(4-bromo-phenyl)-4,7-dichloro-quinazoline (0,085 mmol, 30 mg) [prepared analogously to example 1] in 2 ml THF is treated with benzylamine (0,174 mmol, 0,019 ml). The mixture is heated at 60° for 6 hrs. After cooling to rt, the reaction mixture is filtered through a tentacle ion exchanger (LiChrolut® SCX: Merck ChromBook, 2nd ed. page 31). Evaporation of the solvent afforded benzyl-[2-(4-bromo-phenyl)-7-chloro-quinazolin-4-yl]-amine.

MS calc.: 424,7 ; found: 425.

Example 4:

Analogously to example 3, 2-(4-bromo-phenyl)-4,7-dichloro-quinazoline is reacted

with  $\text{HNR}^2\text{R}^3$  to obtain compounds of formula I1



according to table 2.

Table 2: 4-bromophenyl-quinazolines of formula I1

10

$\text{R}^2$ in $\text{HNR}^2\text{R}^3$ and in I1	$\text{R}^3$ in $\text{HNR}^2\text{R}^3$ and in I1	MS calc.	found
H		438,8	440
H		459,2	460
H		442,7	444
H		442,7	444
H		442,7	444
H		454,8	456
H		473,2	474
H		493,6	494
H		493,6	494

15

20

25

30

5

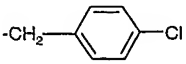
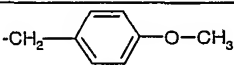
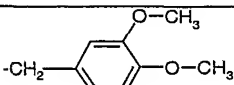
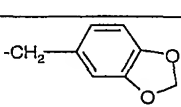
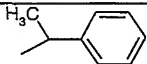
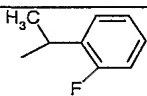
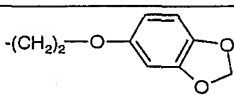
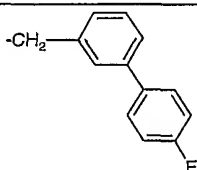
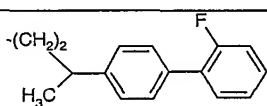
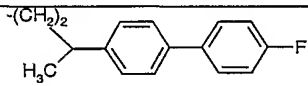
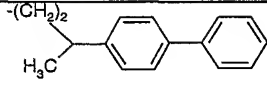
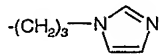
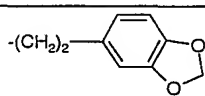
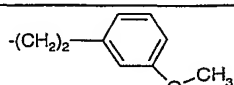
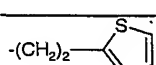
10

15

20

25

30

H		459,2	460
H		454,8	456
H		484,8	486
H		468,7	470
H		438,8	439
H		456,8	457
H		498,8	499
H		518,8	519
H		560,9	561
H		560,9	561
H		542,9	543
H		442,8	444
H		482,8	483
H		468,8	469
H		444,8	445

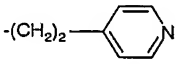
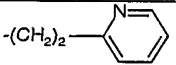
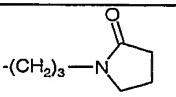
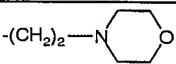
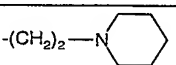
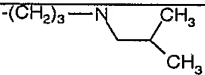
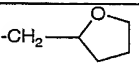
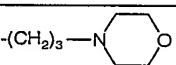
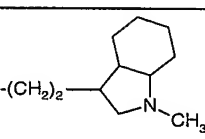
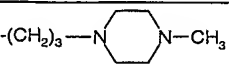
5

10

15

20

25

H		439,8	440
H		439,8	440
H		459,8	460
H		447,8	449
H		445,8	447
H	$-(CH_2)_2-OCH_3$	392,7	393
H	$-(CH_2)_2-N(CH_3)_2$	405,7	405
H	$-(CH_2)_3-N(CH_3)_2$	419,8	420
H	$-(CH_2)_2-N(Et)_2$	433,8	434
H	$-(CH_2)_3-OCH_3$	406,7	407
H		448,8	449
H		418,7	419
H		461,8	462
H		499,9	500
H	Bu	390,7	391
H	Pentyl	404,7	406
H		474,8	475

Example 5:

Analogously to example 3, 2-(4-bromo-phenyl)-4-chloro-6-methyl-quinazoline is reacted

with 1-propyl-pyrrolidin-2-one to obtain

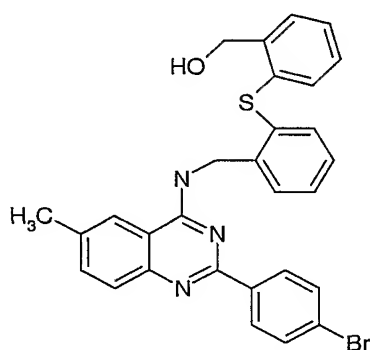
1-{3-[2-(4-bromo-phenyl)-6-methyl-quinazolin-4-ylamino]-propyl}-pyrrolidin-2-one;

MS calc.: 439,4 ; found: 439,6;

5 with [2-(2-aminomethyl-phenylsulfanyl)-phenyl]-methanol to obtain  
[2-(2-{[2-(4-bromo-phenyl)-6-methyl-quinazolin-4-ylamino]-methyl}-phenylsulfanyl)-phenyl]-methanol;

MS calc.: 542,5 ; found: 544,2;

10



15

with 3-(2-methyl-piperidin-1-yl)-propylamine to obtain

[2-(4-bromo-phenyl)-6-methyl-quinazolin-4-yl]-[3-(2-methyl-piperidin-1-yl)-propyl]-amine;

20

MS calc.: 453,4 ; found: 453,3;

with 2-pyridin-2-yl-ethylamine to obtain

[2-(4-bromo-phenyl)-6-methyl-quinazolin-4-yl]-(2-pyridin-2-yl-ethyl)-amine;

25

MS calc.: 419,3 ; found: 419,3;

with 1-(3-trifluoromethyl-phenyl)-piperazine to obtain

2-(4-bromo-phenyl)-6-methyl-4-[4-(3-trifluoromethyl-phenyl)-piperazin-1-yl]-quinazoline;

30

MS calc.: 419,3 ; found: 419,3;

with C-(1-ethyl-pyrrolidin-2-yl)-methylamine to obtain

[2-(4-bromo-phenyl)-6-methyl-quinazolin-4-yl]-(1-ethyl-pyrrolidin-2-ylmethyl)-amine;

MS calc.: 425,4 ; found: 425,6;

5

with 4-benzyl-piperidin-4-ol to obtain

4-benzyl-1-[2-(4-bromo-phenyl)-6-methyl-quinazolin-4-yl]-piperidin-4-ol;

MS calc.: 488,4 ; found: 490,3;

10

with 1-phenyl-piperazine to obtain

2-(4-bromo-phenyl)-6-methyl-4-(4-phenyl-piperazin-1-yl)-quinazoline;

MS calc.: 459,4 ; found: 459,4;

with 3-morpholin-4-yl-propylamine to obtain

15

[2-(4-bromo-phenyl)-6-methyl-quinazolin-4-yl]-(3-morpholin-4-yl-propyl)-amine;

MS calc.: 441,4 ; found: 441,3;

with 2-(1-methyl-pyrrolidin-2-yl)-ethylamine to obtain

20

[2-(4-bromo-phenyl)-6-methyl-quinazolin-4-yl]-[2-(1-methyl-pyrrolidin-2-yl)-ethyl]-amine;

MS calc.: 425,4 ; found: 425,4;

with 3-(4-methyl-piperazin-1-yl)-propylamine to obtain

25

[2-(4-bromo-phenyl)-6-methyl-quinazolin-4-yl]-[3-(4-methyl-piperazin-1-yl)-propyl]-amine;

MS calc.: 454,4 ; found: 454,4;

with 3,4,5-trimethoxy-benzylamine to obtain

30

[2-(4-bromo-phenyl)-6-methyl-quinazolin-4-yl]-(3,4,5-trimethoxy-benzyl)-amine;

MS calc.: 494,4 ; found: 496,1;

with 2-fluoro-benzylamine to obtain

[2-(4-bromo-phenyl)-6-methyl-quinazolin-4-yl]-(2-fluoro-benzyl)-amine;

MS calc.: 422,3 ; found: 422,4;

5

with benzyl-methyl-amine to obtain

benzyl-[2-(4-bromo-phenyl)-6-methyl-quinazolin-4-yl]-methyl-amine;

MS calc.: 418,3 ; found: 418,4;

10

with methyl-(1-methyl-piperidin-4-ylmethyl)-amine to obtain

[2-(4-bromo-phenyl)-6-methyl-quinazolin-4-yl]-methyl-(1-methyl-piperidin-4-ylmethyl)-amine;

MS calc.: 425,3 ; found: 425,2;

15

with cyclohexyl-methyl-amine to obtain

[2-(4-bromo-phenyl)-6-methyl-quinazolin-4-yl]-cyclohexyl-methyl-amine;

MS calc.: 410,4 ; found: 412,1;

with N<sup>1</sup>,N<sup>1</sup>-dimethyl-ethane-1,2-diamine to obtain

20 N'-[2-(4-bromo-phenyl)-6-methyl-quinazolin-4-yl]-N,N-dimethyl-ethane-1,2-diamine;

MS calc.: 385,3 ; found: 386,3;

with butyl-methyl-amine to obtain

25 [2-(4-bromo-phenyl)-6-methyl-quinazolin-4-yl]-butyl-methyl-amine;

MS calc.: 384,3 ; found: 384,4;

with N,N,N'-trimethyl-propane-1,3-diamine to obtain

30 N-[2-(4-bromo-phenyl)-6-methyl-quinazolin-4-yl]-N,N',N'-trimethyl-propane-1,3-diamine;

MS calc.: 413,4 ; found: 415,2;

with 4-benzyl-piperidine to obtain

4-(4-benzyl-piperidin-1-yl)-2-(4-bromo-phenyl)-6-methyl-quinazoline;

MS calc.: 472,4 ; found: 474,3;

5 with N<sup>1</sup>,N<sup>1</sup>-diethyl-pentane-1,4-diamine to obtain

N<sup>4</sup>-[2-(4-bromo-phenyl)-6-methyl-quinazolin-4-yl]-N<sup>1</sup>,N<sup>1</sup>-diethyl-pentane-1,4-diamine;

MS calc.: 455,4 ; found: 455,3;

10 with butylamine to obtain

[2-(4-bromo-phenyl)-6-methyl-quinazolin-4-yl]-butyl-amine;

with N,N-diethyl-propane-1,3-diamine to obtain

15 N'-[2-(4-bromo-phenyl)-6-methyl-quinazolin-4-yl]-N,N-diethyl-propane-1,3-diamine;

with benzylamine to obtain

benzyl-[2-(4-bromo-phenyl)-6-methyl-quinazolin-4-yl]-amine.

20 Example 6:

Analogously to example 3, 2-(4-bromo-phenyl)-4,6-dichloro-quinazoline is reacted

with N<sup>1</sup>,N<sup>1</sup>-diethyl-pentane-1,4-diamine to obtain

25 N<sup>4</sup>-[2-(4-bromo-phenyl)-6-chloro-quinazolin-4-yl]-N<sup>1</sup>,N<sup>1</sup>-diethyl-pentane-1,4-diamine;

MS calc.: 475,86 ; found: 476;

with 4-benzyl-piperidine to obtain

30 4-(4-benzyl-piperidin-1-yl)-2-(4-bromo-phenyl)-6-chloro-quinazoline;

MS calc.: 492,84; found: 493;

with N,N,N'-trimethyl-propane-1,3-diamine to obtain

N-[2-(4-bromo-phenyl)-6-chloro-quinazolin-4-yl]-N,N',N'-trimethyl-propane-1,3-diamine;

MS calc.: 433,78; found: 434;

5

with butyl-methyl-amine to obtain

[2-(4-bromo-phenyl)-6-chloro-quinazolin-4-yl]-butyl-methyl-amine;

MS calc.: 404,74 ; found: 405;

10

with N<sup>1</sup>,N<sup>1</sup>-dimethyl-ethane-1,2-diamine to obtain

N'-[2-(4-bromo-phenyl)-6-chloro-quinazolin-4-yl]-N,N-dimethyl-ethane-1,2-diamine;

with N<sup>1</sup>,N<sup>1</sup>-diethyl-ethane-1,2-diamine to obtain

15

N'-[2-(4-bromo-phenyl)-6-chloro-quinazolin-4-yl]-N,N-diethyl-ethane-1,2-diamine;

with cyclohexyl-methyl-amine to obtain

[2-(4-bromo-phenyl)-6-chloro-quinazolin-4-yl]-cyclohexyl-methyl-amine;

20

MS calc.: 430,77; found: 431;

with methyl-(1-methyl-piperidin-4-ylmethyl)-amine to obtain

[2-(4-bromo-phenyl)-6-chloro-quinazolin-4-yl]-methyl-(1-methyl-piperidin-4-ylmethyl)-amine;

25

MS calc.: 445,79; found: 446;

with benzyl-methyl-amine to obtain

benzyl-[2-(4-bromo-phenyl)-6-chloro-quinazolin-4-yl]-methyl-amine;

MS calc.: 438,75; found: 439;

30

with 2-fluoro-benzylamine to obtain

[2-(4-bromo-phenyl)-6-chloro-quinazolin-4-yl]-(2-fluoro-benzyl)-amine;

MS calc.: 442,72; found: 443;

with 3,4,5-trimethoxy-benzylamine to obtain

5 [2-(4-bromo-phenyl)-6-chloro-quinazolin-4-yl]-(3,4,5-trimethoxy-benzyl)-  
amine;

MS calc.: 514,80; found: 515;

with 3-(4-methyl-piperazin-1-yl)-propylamine to obtain

10 [2-(4-bromo-phenyl)-6-chloro-quinazolin-4-yl]-[3-(4-methyl-piperazin-1-  
yl)-propyl]-amine;

MS calc.: 474,8 ; found: 474;

with 2-(1-methyl-pyrrolidin-2-yl)-ethylamine to obtain

15 [2-(4-bromo-phenyl)-6-chloro-quinazolin-4-yl]-[2-(1-methyl-pyrrolidin-2-  
yl)-ethyl]-amine;

MS calc.: 445,79; found: 446;

with 3-morpholin-4-yl-propylamine to obtain

20 [2-(4-bromo-phenyl)-6-chloro-quinazolin-4-yl]-(3-morpholin-4-yl-propyl)-  
amine;

MS calc.: 461,78; found: 462;

with 1-phenyl-piperazine to obtain

25 2-(4-bromo-phenyl)-6-chloro-4-(4-phenyl-piperazin-1-yl)-quinazoline;  
MS calc.: 479,81; found: 480;

with 4-benzyl-piperidin-4-ol to obtain

30 4-benzyl-1-[2-(4-bromo-phenyl)-6-chloro-quinazolin-4-yl]-piperidin-4-ol;  
MS calc.: 508,84; found: 509;

with C-(1-ethyl-pyrrolidin-2-yl)-methylamine to obtain

[2-(4-bromo-phenyl)-6-chloro-quinazolin-4-yl]-(1-ethyl-pyrrolidin-2-ylmethyl)-amine;

MS calc.: 445,78; found: 446;

5 with 1-(3-trifluoromethyl-phenyl)-piperazine to obtain

2-(4-bromo-phenyl)-6-chloro-4-[4-(3-trifluoromethyl-phenyl)-piperazin-1-yl]-quinazoline;

MS calc.: 547,80; found: 549;

10 with 2-pyridin-2-yl-ethylamine to obtain

[2-(4-bromo-phenyl)-6-chloro-quinazolin-4-yl]-(2-pyridin-2-yl-ethyl)-amine;

MS calc.: 439,74; found: 440;

15 with 3-(2-methyl-piperidin-1-yl)-propylamine to obtain

[2-(4-bromo-phenyl)-6-chloro-quinazolin-4-yl]-[3-(2-methyl-piperidin-1-yl)-propyl]-amine;

MS calc.: 472,83; found: 473;

20 with [2-(2-aminomethyl-phenylsulfanyl)-phenyl]-methanol to obtain

[2-(2-[[2-(4-bromo-phenyl)-6-chloro-quinazolin-4-ylamino]-methyl]-phenylsulfanyl)-phenyl]-methanol;

MS calc.: 562,92; found: 563;

25 with 1-propyl-pyrrolidin-2-one to obtain

1-{3-[2-(4-bromo-phenyl)-6-chloro-quinazolin-4-ylamino]-propyl}-pyrrolidin-2-one;

MS calc.: 459,77; found: 460;

30 with butylamine to obtain

[2-(4-bromo-phenyl)-6-chloro-quinazolin-4-yl]-butyl-amine;

with N,N-diethyl-propane-1,3-diamine to obtain

N'-[2-(4-bromo-phenyl)-6-chloro-quinazolin-4-yl]-N,N-diethyl-propane-1,3-diamine;

5 with benzylamine to obtain

benzyl-[2-(4-bromo-phenyl)-6-chloro-quinazolin-4-yl]-amine.

Example 7:

10 Analogously to example 3, 2-(4-bromo-phenyl)-4-chloro-6,7-dimethoxy-quinazoline is reacted

with 1-propyl-pyrrolidin-2-one to obtain

15 1-{3-[2-(4-bromo-phenyl)-6,7-dimethoxy-quinazolin-4-ylamino]-propyl}-pyrrolidin-2-one;

with [2-(2-aminomethyl-phenylsulfanyl)-phenyl]-methanol to obtain

[2-(2-{[2-(4-bromo-phenyl)-6,7-dimethoxy-quinazolin-4-ylamino]-methyl}-phenylsulfanyl)-phenyl]-methanol;

20 MS calc.: 588,52; found: 589;

with 3-(2-methyl-piperidin-1-yl)-propylamine to obtain

[2-(4-bromo-phenyl)-6,7-dimethoxy-quinazolin-4-yl]-[3-(2-methyl-piperidin-1-yl)-propyl]-amine;

25 MS calc.: 499,45; found: 500;

with 2-pyridin-2-yl-ethylamine to obtain

[2-(4-bromo-phenyl)-6,7-dimethoxy-quinazolin-4-yl]-(2-pyridin-2-yl-ethyl)-amine;

30 MS calc.: 465,35; found: 466;

with 1-(3-trifluoromethyl-phenyl)-piperazine to obtain

2-(4-bromo-phenyl)-6,7-dimethoxy-4-[4-(3-trifluoromethyl-phenyl)-piperazin-1-yl]-quinazoline;

MS calc.: 573,41; found: 574;

5 with C-(1-ethyl-pyrrolidin-2-yl)-methylamine to obtain

[2-(4-bromo-phenyl)-6,7-dimethoxy-quinazolin-4-yl]-(1-ethyl-pyrrolidin-2-ylmethyl)-amine;

MS calc.: 483,41; found: 484;

10 with 4-benzyl-piperidin-4-ol to obtain

4-benzyl-1-[2-(4-bromo-phenyl)-6,7-dimethoxy-quinazolin-4-yl]-piperidin-4-ol;

MS calc.: 534,45; found: 535;

15 with 1-phenyl-piperazine to obtain

2-(4-bromo-phenyl)-6,7-dimethoxy-4-(4-phenyl-piperazin-1-yl)-quinazoline;

MS calc.: 505,41; found: 506;

20 with 3-morpholin-4-yl-propylamine to obtain

[2-(4-bromo-phenyl)-6,7-dimethoxy-quinazolin-4-yl]-(3-morpholin-4-yl-propyl)-amine;

MS calc.: 487,39; found: 488;

25 with 2-(1-methyl-pyrrolidin-2-yl)-ethylamine to obtain

[2-(4-bromo-phenyl)-6,7-dimethoxy-quinazolin-4-yl]-[2-(1-methyl-pyrrolidin-2-yl)-ethyl]-amine;

MS calc.: 471,39; found: 472;

30 with 3-(4-methyl-piperazin-1-yl)-propylamine to obtain

[2-(4-bromo-phenyl)-6,7-dimethoxy-quinazolin-4-yl]-[3-(4-methyl-piperazin-1-yl)-propyl]-amine;

MS calc.: 486,43; found: 487;

with 3,4,5-trimethoxy-benzylamine to obtain

5 [2-(4-bromo-phenyl)-6,7-dimethoxy-quinazolin-4-yl]-(3,4,5-trimethoxy-benzyl)-amine;

MS calc.: 540,41; found: 541;

with 2-fluoro-benzylamine to obtain

10 [2-(4-bromo-phenyl)-6,7-dimethoxy-quinazolin-4-yl]-(2-fluoro-benzyl)-amine;

MS calc.: 468,32; found: 469;

with benzyl-methyl-amine to obtain

15 benzyl-[2-(4-bromo-phenyl)-6,7-dimethoxy-quinazolin-4-yl]-methyl-amine;  
MS calc.: 464,36; found: 465;

with methyl-(1-methyl-piperidin-4-ylmethyl)-amine to obtain

20 [2-(4-bromo-phenyl)-6,7-dimethoxy-quinazolin-4-yl]-methyl-(1-methyl-piperidin-4-ylmethyl)-amine;

MS calc.: 471,40; found: 472;

with cyclohexyl-methyl-amine to obtain

25 [2-(4-bromo-phenyl)-6,7-dimethoxy-quinazolin-4-yl]-cyclohexyl-methyl-amine;

MS calc.: 456,38; found: 457;

with N<sup>1</sup>,N<sup>1</sup>-dimethyl-ethane-1,2-diamine to obtain

30 N'-[2-(4-bromo-phenyl)-6,7-dimethoxy-quinazolin-4-yl]-N,N-dimethyl-ethane-1,2-diamine;

MS calc.: 431,33; found: 432;

with N<sup>1</sup>,N<sup>1</sup>-diethyl-ethane-1,2-diamine to obtain

N'-[2-(4-bromo-phenyl)-6,7-dimethoxy-quinazolin-4-yl]-N,N-diethyl-ethane-1,2-diamine;

with butyl-methyl-amine to obtain

5 [2-(4-bromo-phenyl)-6,7-dimethoxy-quinazolin-4-yl]-butyl-methyl-amine;  
MS calc.: 431,35; found: 432;

with N,N,N'-trimethyl-propane-1,3-diamine to obtain

10 N-[2-(4-bromo-phenyl)-6,7-dimethoxy-quinazolin-4-yl]-N,N',N'-trimethyl-propane-1,3-diamine;  
MS calc.: 459,38; found: 460;

with 4-benzyl-piperidine to obtain

15 4-(4-benzyl-piperidin-1-yl)-2-(4-bromo-phenyl)-6,7-dimethoxy-quinazoline;  
MS calc.: 518,45; found: 519;

with N<sup>1</sup>,N<sup>1</sup>-diethyl-pentane-1,4-diamine to obtain

20 N<sup>4</sup>-[2-(4-bromo-phenyl)-6,7-dimethoxy-quinazolin-4-yl]-N<sup>1</sup>,N<sup>1</sup>-diethyl-pentane-1,4-diamine;  
MS calc.: 501,47; found: 502;

with butylamine to obtain

25 [2-(4-bromo-phenyl)-6,7-dimethoxy-quinazolin-4-yl]-butyl-amine;

with N,N-diethyl-propane-1,3-diamine to obtain

N'-[2-(4-bromo-phenyl)-6,7-dimethoxy-quinazolin-4-yl]-N,N-diethyl-propane-1,3-diamine;

30 with benzylamine to obtain

benzyl-[2-(4-bromo-phenyl)-6,7-dimethoxy-quinazolin-4-yl]-amine.

Example 8:

Analogously to example 3, 2-phenyl-4,7-dichloro-quinazoline [prepared analogously to example 1, starting compounds 2-amino-4-chlorobenzonitrile and benzoylchloride] is reacted

5

with 3-imidazol-1-yl-propylamine to obtain

(7-chloro-2-phenyl-quinazolin-4-yl)-(3-imidazol-1-yl-propyl)-amine;

with N<sup>1</sup>,N<sup>1</sup>-diethyl-pentane-1,4-diamine to obtain

10

N<sup>4</sup>-(7-chloro-2-phenyl-quinazolin-4-yl)-N<sup>1</sup>,N<sup>1</sup>-diethyl-pentane-1,4-diamine;

with 3-morpholin-4-yl-propylamine to obtain

(7-chloro-2-phenyl-quinazolin-4-yl)-(3-morpholin-4-yl-propyl)-amine;

15

with phenyl-amine to obtain

(7-chloro-2-phenyl-quinazolin-4-yl)-phenyl-amine.

Analogously to example 3, N-[4-(4,7-dichloro-quinazolin-2-yl)-phenyl]-3-methyl-butyramide [prepared analogously to example 1, starting compounds 2-amino-4-chlorobenzonitrile and 4-(3-methyl-butyrylamino)-benzoyl chloride] is reacted

20

with N<sup>1</sup>,N<sup>1</sup>-diethyl-propane-1,3-diamine to obtain

25

N-{4-[7-chloro-4-(3-diethylamino-propylamino)-quinazolin-2-yl]-phenyl}-3-methyl-butyramide.

Example 9:

Analogously to example 3, 2-biphenyl-4-yl-4,7-dichloro-quinazoline [prepared analogously to example 1, starting compounds 2-amino-4-chlorobenzonitrile and biphenyl-4-carbonyl chloride] is reacted

30

with N<sup>1</sup>,N<sup>1</sup>-diethyl-pentane-1,4-diamine to obtain

N<sup>4</sup>-(2-biphenyl-4-yl-7-chloro-quinazolin-4-yl)-N<sup>1</sup>,N<sup>1</sup>-diethyl-pentane-1,4-diamine;

5 with 3-imidazol-1-yl-propylamine to obtain

(2-biphenyl-4-yl-7-chloro-quinazolin-4-yl)-(3-imidazol-1-yl-propyl)-amine;

with N<sup>1</sup>,N<sup>1</sup>-diethyl-ethane-1,2-diamine to obtain

10 N'-(2-biphenyl-4-yl-7-chloro-quinazolin-4-yl)-N,N-diethyl-ethane-1,2-diamine;

with N<sup>1</sup>,N<sup>1</sup>-diethyl-propane-1,3-diamine to obtain

N'-(2-biphenyl-4-yl-7-chloro-quinazolin-4-yl)-N,N-diethyl-propane-1,3-diamine;

15 with 3-morpholin-4-yl-propylamine to obtain

(2-biphenyl-4-yl-7-chloro-quinazolin-4-yl)-(3-morpholin-4-yl-propyl)-amine;

20 with 1-(3-amino-propyl)-pyrrolidin-2-one to obtain

1-[3-(2-biphenyl-4-yl-7-chloro-quinazolin-4-ylamino)-propyl]-pyrrolidin-2-one;

with 4-(2-amino-ethyl)-phenylamine to obtain

25 [2-(4-amino-phenyl)-ethyl]-(2-biphenyl-4-yl-7-chloro-quinazolin-4-yl)-amine;

with N<sup>1</sup>-(5-nitro-pyridin-2-yl)-ethane-1,2-diamine to obtain

30 N-(2-biphenyl-4-yl-7-chloro-quinazolin-4-yl)-N'-(5-nitro-pyridin-2-yl)-ethane-1,2-diamine;

with 2-piperazin-1-yl-ethylamine to obtain

(2-biphenyl-4-yl-7-chloro-quinazolin-4-yl)-(2-piperazin-1-yl-ethyl)-amine;

with (4-aminomethyl-phenyl)-dimethyl-amine to obtain

5 (2-biphenyl-4-yl-7-chloro-quinazolin-4-yl)-(4-dimethylamino-benzyl)-  
amine;

with 2-pyridin-2-yl-ethylamine to obtain

(2-biphenyl-4-yl-7-chloro-quinazolin-4-yl)-(2-pyridin-2-yl-ethyl)-amine;

10 with C-(3-aminomethyl-cyclohexyl)-methylamine to obtain

(3-aminomethyl-cyclohexylmethyl)-(2-biphenyl-4-yl-7-chloro-quinazolin-4-yl)-amine;

with heptane-1,7-diamine to obtain

15 N<sup>1</sup>-(2-biphenyl-4-yl-7-chloro-quinazolin-4-yl)-heptane-1,7-diamine;

with propane-1,3-diamine to obtain

N<sup>1</sup>-(2-biphenyl-4-yl-7-chloro-quinazolin-4-yl)-propane-1,3-diamine.

20 Example 10:

Analogously to example 3, 2-(4-bromo-phenyl)-4,7-dichloro-quinazoline [prepared analogously to example 1, starting compounds 2-amino-4-chlorobenzonitrile and 4-bromobenzoylchloride] is reacted with

N<sup>1</sup>,N<sup>1</sup>-diethyl-propane-1,3-diamine to obtain

25 N'-[2-(4-bromo-phenyl)-7-chloro-quinazolin-4-yl]-N,N-diethyl-propane-1,3-diamine.

1,2 Equivalents of K<sub>2</sub>CO<sub>3</sub>, 1,2 equivalents of 4-chlorophenylboronic acid and 10 mol% of Pd((PPh<sub>3</sub>)<sub>4</sub>) are added to a solution of N'-[2-(4-bromo-phenyl)-7-chloro-quinazolin-4-yl]-N,N-diethyl-propane-1,3-diamine (16,5 mmol) in 80 ml of DMF and it is heated at 80° until conversion is complete. After filtering off the catalyst and customary working up for solution

30

reactions, N'-[7-chloro-2-(4'-chloro-biphenyl-4-yl)-quinazolin-4-yl]-N,N-diethyl-propane-1,3-diamine is obtained.

Example 11:

5 Analogously to example 10, N'-[2-(4-bromo-phenyl)-7-chloro-quinazolin-4-yl]-N,N-diethyl-propane-1,3-diamine is reacted

with 4-methoxyphenylboronic acid to obtain

10 N'-[7-chloro-2-(4'-methoxy-biphenyl-4-yl)-quinazolin-4-yl]-N,N-diethyl-propane-1,3-diamine;

with 3-acetylaminophenylboronic acid to obtain

15 N-{4'-[7-chloro-4-(3-diethylamino-propylamino)-quinazolin-2-yl]-biphenyl-3-yl}-acetamide;

with 3-formylphenylboronic acid to obtain

20 4'-[7-chloro-4-(3-diethylamino-propylamino)-quinazolin-2-yl]-biphenyl-3-carbaldehyde;

with 4-[(cyclohexylmethyl-amino)-methyl]-phenylboronic acid to obtain

25 N-(7-chloro-2-{4'-[(cyclohexylmethyl-amino)-methyl]-biphenyl-4-yl}-quinazolin-4-yl)-N',N'-diethyl-propane-1,3-diamine.

25 Analogously to example 10, N'-[2-(3-bromo-phenyl)-7-chloro-quinazolin-4-yl]-N,N-diethyl-propane-1,3-diamine is reacted

with 3,5-dichlorophenylboronic acid to obtain

30 N'-[7-chloro-2-(3',5'-dichloro-biphenyl-3-yl)-quinazolin-4-yl]-N,N-diethyl-propane-1,3-diamine;

with 4-fluorophenylboronic acid to obtain

N'-[7-chloro-2-(4'-fluoro-biphenyl-3-yl)-quinazolin-4-yl]-N,N-diethylpropane-1,3-diamine.

Example 12:

5 Analogously to example 10, N<sup>4</sup>-[2-(4-bromo-phenyl)-7-chloro-quinazolin-4-yl]-N<sup>1</sup>,N<sup>1</sup>-diethyl-pentane-1,4-diamine (prepared according to example 3) is reacted

with 4-chlorophenylboronic acid to obtain

10 N<sup>4</sup>-[7-chloro-2-(4'-chloro-biphenyl-4-yl)-quinazolin-4-yl]-N<sup>1</sup>,N<sup>1</sup>-diethyl-pentane-1,4-diamine;

with 3-formylphenylboronic acid to obtain

15 4'-[7-chloro-4-(4-diethylamino-1-methyl-butylamino)-quinazolin-2-yl]-biphenyl-3-carbaldehyde;

with 3-[(hydroxypropyl-amino)-methyl]-phenylboronic acid to obtain

20 3-({4'-[7-chloro-4-(4-diethylamino-1-methyl-butylamino)-quinazolin-2-yl]-biphenyl-3-ylmethyl}-amino)-propan-1-ol.

Analogously to example 10, N<sup>4</sup>-[2-(3-bromo-phenyl)-7-chloro-quinazolin-4-yl]-N<sup>1</sup>,N<sup>1</sup>-diethyl-pentane-1,4-diamine is reacted

with 4-methoxyphenylboronic acid to obtain

25 N<sup>4</sup>-[7-chloro-2-(4'-methoxy-biphenyl-3-yl)-quinazolin-4-yl]-N<sup>1</sup>,N<sup>1</sup>-diethyl-pentane-1,4-diamine;

with (pyridin-3-yl)boronic acid to obtain

30 N<sup>4</sup>-[7-chloro-2-(3-pyridin-3-yl-phenyl)-quinazolin-4-yl]-N<sup>1</sup>,N<sup>1</sup>-diethyl-pentane-1,4-diamine.

Example 13:

Analogously to example 3, 2-(4-bromo-phenyl)-4,7-dichloro-quinazoline [prepared analogously to example 1, starting compounds 2-amino-4-chlorobenzonitrile and 4-bromobenzoylchloride] is reacted with 2-(1-methyl-octahydro-indol-3-yl)-ethylamine to obtain

5 [2-(4-bromo-phenyl)-7-chloro-quinazolin-4-yl]-[2-(1-methyl-octahydro-indol-3-yl)-ethyl]-amine.

Analogously to example 10, [2-(4-bromo-phenyl)-7-chloro-quinazolin-4-yl]-[2-(1-methyl-octahydro-indol-3-yl)-ethyl]-amine is reacted

10 with 4-fluorophenylboronic acid to obtain

[7-chloro-2-(4'-fluoro-biphenyl-4-yl)-quinazolin-4-yl]-[2-(1-methyl-octahydro-indol-3-yl)-ethyl]-amine;

15 with (thiophen-2-yl)boronic acid to obtain

[7-chloro-2-(4-thiophen-2-yl-phenyl)-quinazolin-4-yl]-[2-(1-methyl-octahydro-indol-3-yl)-ethyl]-amine;

with (pyridin-3-yl)boronic acid to obtain

20 [7-chloro-2-(4-pyridin-3-yl-phenyl)-quinazolin-4-yl]-[2-(1-methyl-octahydro-indol-3-yl)-ethyl]-amine.

Analogously to example 10, [2-(3-bromo-phenyl)-7-chloro-quinazolin-4-yl]-[2-(1-methyl-octahydro-indol-3-yl)-ethyl]-amine is reacted

25 with (thiophen-2-yl)boronic acid to obtain

[7-chloro-2-(3-thiophen-2-yl-phenyl)-quinazolin-4-yl]-[2-(1-methyl-octahydro-indol-3-yl)-ethyl]-amine;

with 3-(acetylamino)-phenylboronic acid to obtain

30 N-(3'-(7-chloro-4-[2-(1-methyl-octahydro-indol-3-yl)-ethylamino]-quinazolin-2-yl)-biphenyl-3-yl)-formamide.

Example 14:

Analogously to example 3, 2-(4-bromo-phenyl)-4,7-dichloro-quinazoline [prepared analogously to example 1, starting compounds 2-amino-4-chlorobenzonitrile and 4-bromobenzoylchloride] is reacted with 2-(1-methyl-piperidin-3-yl)-ethylamine to obtain  
5 [7-chloro-2-(4-bromo-phenyl)-quinazolin-4-yl]-[2-(1-methyl-piperidin-3-yl)-ethyl]-amine.

Analogously to example 10, [7-chloro-2-(4-bromo-phenyl)-quinazolin-4-yl]-  
10 [2-(1-methyl-piperidin-3-yl)-ethyl]-amine is reacted

with 3-formylphenylboronic acid to obtain

4'-[7-chloro-4-[2-(1-methyl-piperidin-3-yl)-ethylamino]-quinazolin-2-yl]-  
biphenyl-3-carbaldehyde;  
15

with (thiophen-3-yl)boronic acid to obtain

[7-chloro-2-(4-thiophen-3-yl-phenyl)-quinazolin-4-yl]-[2-(1-methyl-piperidin-3-yl)-ethyl]-amine;

20 with 2-(formyl-thiophen-3-yl)boronic acid to obtain

3-(4-{7-chloro-4-[2-(1-methyl-piperidin-3-yl)-ethylamino]-quinazolin-2-yl}-phenyl)-thiophene-2-carbaldehyde;

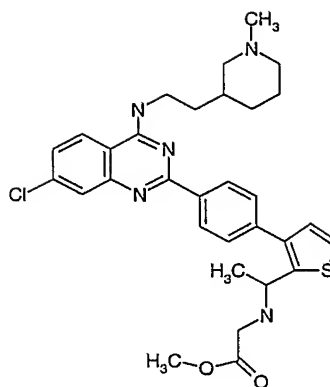
with 3-[(2-methoxy-ethylamino)-methyl]-phenylboronic acid to obtain

25 (7-chloro-2-{3'-[(2-methoxy-ethylamino)-methyl]-biphenyl-4-yl}-quinazolin-4-yl)-[2-(1-methyl-piperidin-3-yl)-ethyl]-amine;

with {2-[1-(methoxycarbonylmethyl-amino)-ethyl]-thiophen-3-yl}-boronic acid to obtain

30 {1-[3-(4-{7-chloro-4-[2-(1-methyl-piperidin-3-yl)-ethylamino]-quinazolin-2-yl}-phenyl)-thiophen-2-yl]-ethylamino}-acetic acid methyl ester

5



10 Analogously to example 3, 2-(4-bromo-phenyl)-4,7-dichloro-quinazoline [prepared analogously to example 1] is reacted with 2-morpholin-4-yl-ethylamine to obtain  
[2-(4-bromo-phenyl)-7-chloro-quinazolin-4-yl]-(2-morpholin-4-yl-ethyl)-amine.

15

Analogously to example 10, [2-(4-bromo-phenyl)-7-chloro-quinazolin-4-yl]-(2-morpholin-4-yl-ethyl)-amine is reacted

with 3,4-dimethoxyphenylboronic acid to obtain

20 [7-chloro-2-(3',4'-dimethoxy-biphenyl-4-yl)-quinazolin-4-yl]-(2-morpholin-4-yl-ethyl)-amine;

with 4-formylphenylboronic acid to obtain

25 4'-[7-chloro-4-(2-morpholin-4-yl-ethylamino)-quinazolin-2-yl]-biphenyl-4-carbaldehyde;

with 2-(formyl-thiophen-3-yl)boronic acid to obtain

3-{4-[7-chloro-4-(2-morpholin-4-yl-ethylamino)-quinazolin-2-yl]-phenyl}-thiophene-2-carbaldehyde;

30

with 4-(propylaminomethyl)-phenylboronic acid to obtain

[7-chloro-2-(4'-propylaminomethyl-biphenyl-4-yl)-quinazolin-4-yl]-(2-morpholin-4-yl-ethyl)-amine.

Example 15:

5 Analogously to example 3, 2-(5-bromo-thiophen-2-yl)-4,7-dichloro-quinazoline [prepared analogously to example 1, starting compounds 2-amino-4-chlorobenzonitrile and 5-bromo-thiophene-2-carbonyl chloride] is reacted with 2-(1-methyl-octahydro-indol-3-yl)-ethylamine to obtain  
10 [2-(5-bromo-thiophen-2-yl)-7-chloro-quinazolin-4-yl]-[2-(1-methyl-octahydro-indol-3-yl)-ethyl]-amine.

Analogously to example 10, [2-(5-bromo-thiophen-2-yl)-7-chloro-quinazolin-4-yl]-[2-(1-methyl-octahydro-indol-3-yl)-ethyl]-amine is reacted

15 with 4-fluorophenylboronic acid to obtain  
{7-chloro-2-[5-(4-fluoro-phenyl)-thiophen-2-yl]-quinazolin-4-yl}-[2-(1-methyl-octahydro-indol-3-yl)-ethyl]-amine;

with 2-methoxyphenylboronic acid to obtain  
20 {7-chloro-2-[5-(2-methoxy-phenyl)-thiophen-2-yl]-quinazolin-4-yl}-[2-(1-methyl-octahydro-indol-3-yl)-ethyl]-amine;

with (1H-indol-5-yl)boronic acid to obtain  
25 {7-chloro-2-[5-(1H-indol-5-yl)-thiophen-2-yl]-quinazolin-4-yl}-[2-(1-methyl-octahydro-indol-3-yl)-ethyl]-amine;

with (quinolin-8-yl)boronic acid to obtain  
[7-chloro-2-(5-quinolin-8-yl-thiophen-2-yl)-quinazolin-4-yl]-[2-(1-methyl-octahydro-indol-3-yl)-ethyl]-amine.  
30

Analogously to example 3, 2-(5-bromo-thiophen-2-yl)-4,7-dichloro-quinazoline [prepared analogously to example 1] is reacted with N<sup>1</sup>,N<sup>1</sup>-diethyl-propane-1,3-diamine to obtain N'-[2-(5-bromo-thiophen-2-yl)-7-chloro-quinazolin-4-yl]-N,N-diethyl-propane-1,3-diamine.

Analogously to example 10, N'-[2-(5-bromo-thiophen-2-yl)-7-chloro-quinazolin-4-yl]-N,N-diethyl-propane-1,3-diamine is reacted

with (thiophen-2-yl)boronic acid to obtain

N'-(2-[2,2']bithiophenyl-5-yl-7-chloro-quinazolin-4-yl)-N,N-diethyl-propane-1,3-diamine;

with (pyridin-4-yl)boronic acid to obtain

N'-[7-chloro-2-(5-pyridin-4-yl-thiophen-2-yl)-quinazolin-4-yl]-N,N-diethyl-propane-1,3-diamine;

with (2,5-dimethoxy)phenylboronic acid to obtain

N'-{7-chloro-2-[5-(2,5-dimethoxy-phenyl)-thiophen-2-yl]-quinazolin-4-yl}-N,N-diethyl-propane-1,3-diamine.

Analogously to example 3, 2-(5-bromo-thiophen-2-yl)-4,7-dichloro-quinazoline [prepared analogously to example 1] is reacted with N<sup>1</sup>,N<sup>1</sup>-diethyl-pentane-1,4-diamine to obtain N<sup>4</sup>-[2-(5-bromo-thiophen-2-yl)-7-chloro-quinazolin-4-yl]-N<sup>1</sup>,N<sup>1</sup>-diethyl-pentane-1,4-diamine.

Analogously to example 10, N<sup>4</sup>-[2-(5-bromo-thiophen-2-yl)-7-chloro-quinazolin-4-yl]-N<sup>1</sup>,N<sup>1</sup>-diethyl-pentane-1,4-diamine is reacted

with 2-cyanophenylboronic acid to obtain

2-{5-[7-chloro-4-(4-diethylamino-1-methyl-butylamino)-quinazolin-2-yl]-thiophen-2-yl}-benzonitrile;

with (benzo[b]thiophen-2-yl)boronic acid to obtain

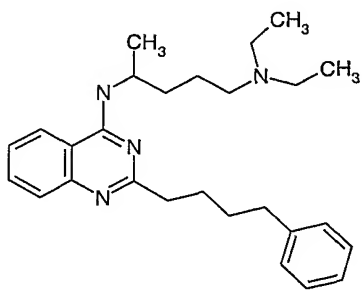
5       $N^4$ -[2-(5-benzo[b]thiophen-2-yl-thiophen-2-yl)-7-chloro-quinazolin-4-yl]- $N^1,N^1$ -diethyl-pentane-1,4-diamine.

Example 16:

10      Analogously to example 3, 4-chloro-2-(4-phenyl-butyl)-quinazoline [prepared analogously to example 1, starting compounds 2-amino-benzonitrile and 5-phenyl-pentanoyl chloride] is reacted

with  $N^1,N^1$ -diethyl-pentane-1,4-diamine to obtain

15       $N^1,N^1$ -diethyl- $N^4$ -[2-(4-phenyl-butyl)-quinazolin-4-yl]-pentane-1,4-diamine;



with C-(3-aminomethyl-cyclohexyl)-methylamine to obtain

25      (3-aminomethyl-cyclohexylmethyl)-[2-(4-phenyl-butyl)-quinazolin-4-yl]-amine;

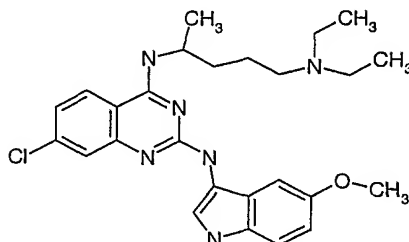
MS      calc.: 402,6 ; found: 403,6.

Example 17:

30      1. A solution of 2,4,7-trichloro-quinazoline (38,7 mmol) in 50 ml DMF is treated with  $N^1,N^1$ -diethyl-pentane-1,4-diamine (50 mmol). The mixture is stirred at rt for 4 hrs. A solution of C-(5-methoxy-1H-indol-3-yl)-methylamine (50 mmol) in 10 ml DMF is added and the mixture is heated to 80-100° for

3 days. Customary working up gives 7-chloro-N<sup>4</sup>-(4-diethylamino-1-methyl-butyl)-N<sup>2</sup>-(5-methoxy-1H-indol-3-ylmethyl)-quinazoline-2,4-diamine

5



10

Analogously to example 17, 2,4,7-trichloro-quinazoline is reacted with N<sup>1</sup>,N<sup>1</sup>-diethyl-pentane-1,4-diamine to give N<sup>4</sup>-(2,7-dichloro-quinazolin-4-yl)-N<sup>1</sup>,N<sup>1</sup>-diethyl-pentane-1,4-diamine and is further reacted

15

with 5-bromo-2-fluoro-benzylamine to obtain

N<sup>2</sup>-(5-bromo-2-fluoro-benzyl)-7-chloro-N<sup>4</sup>-(4-diethylamino-1-methyl-butyl)-quinazoline-2,4-diamine;

20

with 3,5-bis-trifluoromethyl-benzylamine to obtain

N<sup>2</sup>-(3,5-bis-trifluoromethyl-benzyl)-7-chloro-N<sup>4</sup>-(4-diethylamino-1-methyl-butyl)-quinazoline-2,4-diamine;

25

Analogously to example 17, 2,4,7-trichloro-quinazoline is reacted with 2-pyridin-2-yl-ethylamine to give (7-chloro-quinazolin-4-yl)-(2-pyridin-2-yl-ethyl)-amine and is further reacted

30

with phenethylamine to obtain

7-chloro-N<sup>2</sup>-phenethyl-N<sup>4</sup>-(2-pyridin-2-yl-ethyl)-quinazoline-2,4-diamine;

with 3-morpholin-4-yl-propylamine to obtain

7-chloro-N<sup>2</sup>-(3-morpholin-4-yl-propyl)-N<sup>4</sup>-(2-pyridin-2-yl-ethyl)-quinazoline-2,4-diamine.

- 5 Analogously to example 17, 2,4,7-trichloro-quinazoline is reacted with diethylamine to give (2,7-dichloro-quinazolin-4-yl)-diethyl-amine and is further reacted

with biphenyl-4-ylamine to obtain

- 10 N<sup>2</sup>-biphenyl-4-yl-7-chloro-N<sup>4</sup>,N<sup>4</sup>-diethyl-quinazoline-2,4-diamine.

The following examples relate to pharmaceutical preparations:

**Example A: Injection vials**

- 15 A solution of 100 g of an active compound of the formula I and 5 g of disodium hydrogenphosphate is adjusted to pH 6.5 in 3 l of double-distilled water using 2N hydrochloric acid, sterile-filtered, dispensed into injection vials, lyophilized under sterile conditions and aseptically sealed. Each injection vial contains 5 mg of active compound.

20 **Example B: Suppositories**

A mixture of 20 g of an active compound of the formula I is melted with 100 g of soya lecithin and 1400 g of cocoa butter, poured into moulds and allowed to cool. Each suppository contains 20 mg of active compound.

25 **Example C: Solution**

- A solution is prepared from 1 g of an active compound of the formula I, 9.38 g of NaH<sub>2</sub>PO<sub>4</sub>·2H<sub>2</sub>O, 28.48 g of Na<sub>2</sub>HPO<sub>4</sub>·12H<sub>2</sub>O and 0.1 g of benzalkonium chloride in 940 ml of double-distilled water. The mixture is adjusted to pH 6.8, made up to 1 l and sterilized by irradiation. This solution  
30 can be used in the form of eye drops.

**Example D: Ointment**

500 mg of an active compound of the formula I is mixed with 99.5 g of petroleum jelly under aseptic conditions.

**Example E: Tablets**

5 A mixture of 1 kg of active compound of the formula I, 4 kg of lactose, 1.2 kg of potato starch, 0.2 g of talc and 0.1 kg of magnesium stearate is compressed in a customary manner to give tablets such that each tablet contains 10 mg of active compound.

10 **Example F: Coated tablets**

Analogously to Example E, tablets are pressed which are then coated with a coating of sucrose, potato starch, talc, tragacanth and colorant in a customary manner.

15 **Example G: Capsules**

2 kg of active compound of the formula I are dispensed into hard gelatin capsules in a customary manner such that each capsule contains 20 mg of the active compound.

20 **Example H: Ampoules**

A solution of 1 kg of active compound of the formula I in 60 ml of double-distilled water is sterile-filtered, dispensed into ampoules, lyophilized under sterile conditions and aseptically sealed. Each ampule contains 10 mg of active compound.

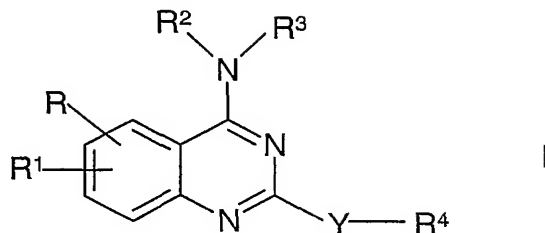
25

30

## What is claimed is:

## 1. Compounds of the formula I

5



in which

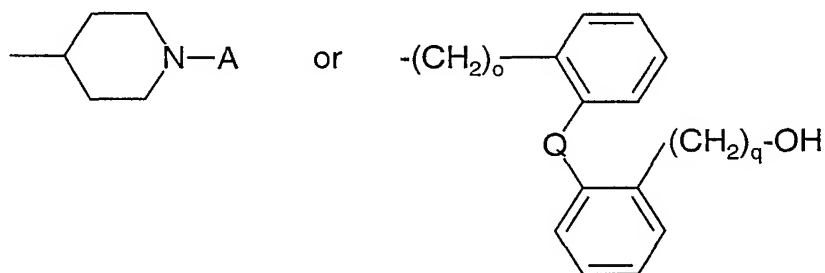
10

R and R<sup>1</sup> are independently of each other H, A, OH, OA, Hal, N(R<sup>5</sup>)<sub>2</sub>, NO<sub>2</sub>, CN, CHO, COA, CON(R<sup>5</sup>)<sub>2</sub>, COOR<sup>5</sup>, allyl, CH=CH-COOR<sup>5</sup>, CH=CHCON(R<sup>5</sup>)<sub>2</sub>, SO<sub>2</sub>A or phenyl, which is unsubstituted or mono-, di- or trisubstituted by A,

15

R<sup>2</sup> and R<sup>3</sup> are independently of each other H, A, cycloalkyl, -Het<sup>3</sup>, -(CH<sub>2</sub>)<sub>o</sub>-OR<sup>5</sup>, -(CH<sub>2</sub>)<sub>o</sub>-OR<sup>6</sup>, -(CH<sub>2</sub>)<sub>o</sub>-Het, -(CH<sub>2</sub>)<sub>o</sub>-NR<sup>5</sup>-Het, -(CHA)<sub>p</sub>-(CH<sub>2</sub>)<sub>o</sub>-N(R<sup>5</sup>)<sub>2</sub>, -(CH<sub>2</sub>)<sub>p</sub>-(CHA)<sub>p</sub>-(CH<sub>2</sub>)<sub>m</sub>-Ar, -(CH<sub>2</sub>)<sub>o</sub>-Z-(CH<sub>2</sub>)<sub>q</sub>-N(R<sup>5</sup>)<sub>2</sub>,

20



25

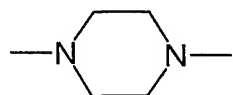
provided that R<sup>2</sup> and R<sup>3</sup> together are not H, or NR<sup>2</sup>R<sup>3</sup> together form a saturated monocyclic heterocyclic radical having 5 to 6 ring members, where 1 or 2 N atoms are present and the heterocyclic radical can be mono- or disubstituted by OH, Ar, OAr or arylalkyl,

30

R<sup>4</sup> is Ar or Het<sup>1</sup>,  
 R<sup>5</sup> is H or A,  
 R<sup>6</sup> is benzo[1,3]dioxol-5-yl,  
 R<sup>7</sup> is H, A, cycloalkyl or (CH<sub>2</sub>)<sub>q</sub>-OR<sup>5</sup>,

Q is O or S,  
 Y is a direct bond,  $(\text{CH}_2)_n$  or  $-\text{NR}^5-(\text{CH}_2)_m-$ ,  
 Z is phenylene, cyclohexylene,  $-\text{NR}^5-$ , O,  $-\text{CH}(\text{OH})-$ ,  $-\text{CA}_2-$  or

5



A is unbranched or branched alkyl having 1 to 6 carbon atoms,  
 Ar is phenyl, naphthyl or biphenyl, which is unsubstituted or  
 mono-, di- or trisubstituted by A, OH, OA, cycloalkyloxy,  
 O- $(\text{CH}_2)_p$ -Ph,  $\text{CF}_3$ ,  $\text{OCF}_3$ , Hal, CN, CHO, COA,  $\text{COOR}^5$ ,  
 10  $-(\text{CH}_2)_p-\text{N}(\text{R}^7)_2$ ,  $\text{NR}^5$ -COA,  $\text{NO}_2$ ,  $\text{SO}_2\text{N}(\text{R}^5)_2$ , mor,  $\text{SO}_2$ -mor,  
 5-methyl-3-oxo-2,4-dihydropyrazol-2-yl, naphthyl or  $\text{Het}^2$ ,  
 Het is a saturated, partially or completely unsaturated mono- or  
 bicyclic heterocyclic radical having 5 to 10 ring members,  
 15 where 1 or 2 N and/or 1 or 2 S or O atoms can be present and  
 the heterocyclic radical can be mono- or disubstituted by A,  
 Hal, OH, OA,  $\text{CF}_3$ ,  $\text{OCF}_3$ ,  $\text{N}(\text{R}^5)_2$ , carbonyl oxygen,  $\text{COOR}^5$ ,  
 benzyl,  $\text{Het}^2$  or phenyl which is unsubstituted or mono-, di- or  
 trisubstituted by A, OH, OA,  $\text{CF}_3$ ,  $\text{OCF}_3$ , Hal, CN,  $\text{COOR}^5$ ,  
 20  $\text{N}(\text{R}^5)_2$ ,  $\text{NO}_2$ ,  $\text{SO}_2\text{N}(\text{R}^5)_2$ ,  
 $\text{Het}^1$  is thiophen-2-yl substituted with Ar or  $\text{Het}^2$ ,  
 $\text{Het}^2$  is a unsaturated mono- or bicyclic heterocyclic radical having  
 5 to 10 ring members, where 1 or 2 N and/or 1 or 2 S or  
 O atoms can be present and the heterocyclic radical can be  
 25 mono- or disubstituted by A, Hal, OH, OA,  $\text{CF}_3$ ,  $\text{OCF}_3$ ,  $\text{N}(\text{R}^5)_2$ ,  
 $-(\text{CH}_2)_p-(\text{CHA})_p-\text{N}(\text{R}^5)-(\text{CH}_2)_q-\text{COR}^5$ , CHO, COA or  $\text{COOR}^5$ ,  
 $\text{Het}^3$  is a partially or completely unsaturated mono- or bicyclic  
 heterocyclic radical having 5 to 10 ring members, where 1 or 2  
 N atoms are present and the heterocyclic radical can be  
 30 mono- or disubstituted by A, Hal, OH, OA,  $\text{CF}_3$ ,  $\text{OCF}_3$ ,  $\text{N}(\text{R}^5)_2$ ,  
 $\text{SO}_2\text{A}$  or  $\text{COOR}^5$  provided that the heterocyclic radical is not  
 bondend via an N atom,

Hal is F, Cl, Br or I,  
mor is morpholin-4-yl,  
Ph is phenyl,  
n is 1, 2, 3, 4, 5 or 6,  
5 m is 0, 1, 2, 3, 4, 5 or 6,  
o is 1, 2, 3, 4, 5, 6 or 7,  
p is 0, 1, 2, 3 or 4,  
q is 1, 2, 3 or 4,

and their pharmaceutically tolerable salts and solvates.

10

2. A compound of claim 1, wherein R is H or OA.

3. A compound according to claims 1 or 2, wherein R<sup>1</sup> is H, A, OA or Hal.

15

4. A compound according to at least one of claims 1 to 3, wherein Y is (CH<sub>2</sub>)<sub>n</sub> and n is 1, 2, 3, 4, 5 or 6.

5. A compound according to at least one of claims 1 to 3, wherein Y is a direct bond.

20

6. A compound according to at least one of claims 1 to 3, wherein Y is -N(R<sup>5</sup>)-(CH<sub>2</sub>)<sub>m</sub>- and R<sup>5</sup> is H or A.

25

7. Compounds of the formula I according to at least one of claims 1 to 6

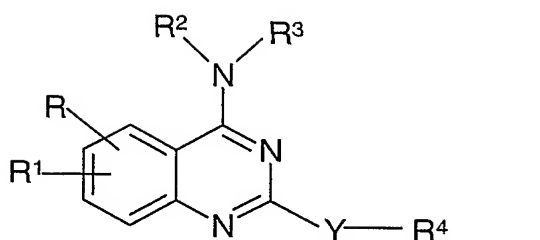
a) [2-(benzo[1,3]dioxol-5-yloxy)-ethyl]-[2-(4-bromo-phenyl)-7-chloro-quinazolin-4-yl]-amine,

b) [2-(4-bromo-phenyl)-7-chloro-quinazolin-4-yl]-[2-(1-methyl-octahydro-indol-3-yl)-ethyl]-amine,

and their physiologically acceptable salts and solvates.

30

8. Process for the preparation of the compounds of the formula I



5

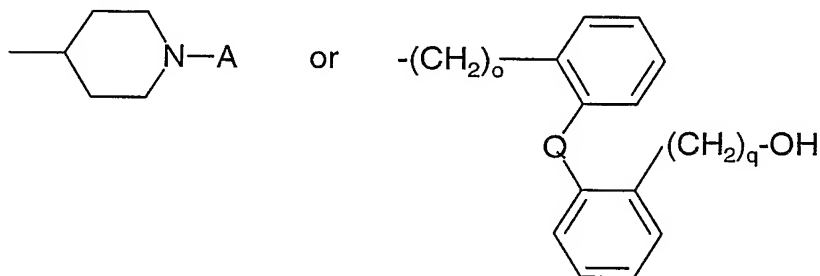
in which

R and R<sup>1</sup> are independently of each other H, A, OH, OA, Hal, N(R<sup>5</sup>)<sub>2</sub>, NO<sub>2</sub>, CN, CHO, COA, CON(R<sup>5</sup>)<sub>2</sub>, COOR<sup>5</sup>, allyl, CH=CH-COOR<sup>5</sup>, CH=CHCON(R<sup>5</sup>)<sub>2</sub>, SO<sub>2</sub>A or phenyl, which is unsubstituted or mono-, di- or trisubstituted by A,

10

R<sup>2</sup> and R<sup>3</sup> are independently of each other H, A, cycloalkyl, -Het<sup>3</sup>, -(CH<sub>2</sub>)<sub>o</sub>-OR<sup>5</sup>, -(CH<sub>2</sub>)<sub>o</sub>-OR<sup>6</sup>, -(CH<sub>2</sub>)<sub>o</sub>-Het, -(CH<sub>2</sub>)<sub>o</sub>-NR<sup>5</sup>-Het, -(CHA)<sub>p</sub>-(CH<sub>2</sub>)<sub>o</sub>-N(R<sup>5</sup>)<sub>2</sub>, -(CH<sub>2</sub>)<sub>p</sub>-(CHA)<sub>p</sub>-(CH<sub>2</sub>)<sub>m</sub>-Ar, -(CH<sub>2</sub>)<sub>o</sub>-Z-(CH<sub>2</sub>)<sub>q</sub>-N(R<sup>5</sup>)<sub>2</sub>,

15



20

provided that R<sup>2</sup> and R<sup>3</sup> together are not H, or NR<sup>2</sup>R<sup>3</sup> together form a saturated monocyclic heterocyclic radical having 5 to 6 ring members, where 1 or 2 N atoms are present and the heterocyclic radical can be mono- or disubstituted by OH, Ar, OAr or arylalkyl,

25

R<sup>4</sup> is Ar or Het<sup>1</sup>,

R<sup>5</sup> is H or A,

R<sup>6</sup> is benzo[1,3]dioxol-5-yl,

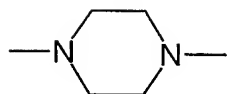
R<sup>7</sup> is H, A, cycloalkyl or -(CH<sub>2</sub>)<sub>q</sub>-OR<sup>5</sup>,

30

Q is O or S,

Y is a direct bond, (CH<sub>2</sub>)<sub>n</sub> or -NR<sup>5</sup>-(CH<sub>2</sub>)<sub>m</sub>-,

Z is phenylene, cyclohexylene, -NR<sup>5</sup>-, O, -CH(OH)-, -CA<sub>2</sub>- or



- 5      A      is unbranched or branched alkyl having 1 to 6 carbon atoms,  
       Ar      is phenyl, naphthyl or biphenyl, which is unsubstituted or  
               mono-, di- or trisubstituted by A, OH, OA, cycloalkyloxy,  
               O-(CH<sub>2</sub>)<sub>p</sub>-Ph, CF<sub>3</sub>, OCF<sub>3</sub>, Hal, CN, CHO, COA, COOR<sup>5</sup>,  
               -(CH<sub>2</sub>)<sub>p</sub>-N(R<sup>7</sup>)<sub>2</sub>, NR<sup>5</sup>-COA, NO<sub>2</sub>, SO<sub>2</sub>N(R<sup>5</sup>)<sub>2</sub>, mor, SO<sub>2</sub>-mor,  
               5-methyl-3-oxo-2,4-dihydropyrazol-2-yl, naphthyl or Het<sup>2</sup>,  
 10      Het      is a saturated, partially or completely unsaturated mono- or  
               bicyclic heterocyclic radical having 5 to 10 ring members,  
               where 1 or 2 N and/or 1 or 2 S or O atoms can be present and  
               the heterocyclic radical can be mono- or disubstituted by A,  
               Hal, OH, OA, CF<sub>3</sub>, OCF<sub>3</sub>, N(R<sup>5</sup>)<sub>2</sub>, carbonyl oxygen, COOR<sup>5</sup>,  
 15      benzyl, Het<sup>2</sup> or phenyl which is unsubstituted or mono-, di- or  
               trisubstituted by A, OH, OA, CF<sub>3</sub>, OCF<sub>3</sub>, Hal, CN, COOR<sup>5</sup>,  
               N(R<sup>5</sup>)<sub>2</sub>, NO<sub>2</sub>, SO<sub>2</sub>N(R<sup>5</sup>)<sub>2</sub>,  
       Het<sup>1</sup>      is thiophen-2-yl substituted with Ar or Het<sup>2</sup>,  
       Het<sup>2</sup>      is a unsaturated mono- or bicyclic heterocyclic radical having  
 20      5 to 10 ring members, where 1 or 2 N and/or 1 or 2 S or  
               O atoms can be present and the heterocyclic radical can be  
               mono- or disubstituted by A, Hal, OH, OA, CF<sub>3</sub>, OCF<sub>3</sub>, N(R<sup>5</sup>)<sub>2</sub>,  
               -(CH<sub>2</sub>)<sub>p</sub>-(CHA)<sub>p</sub>-N(R<sup>5</sup>)-(CH<sub>2</sub>)<sub>q</sub>-COR<sup>5</sup>, CHO, COA or COOR<sup>5</sup>,  
       Het<sup>3</sup>      is a partially or completely unsaturated mono- or bicyclic  
 25      heterocyclic radical having 5 to 10 ring members, where 1 or 2  
               N atoms are present and the heterocyclic radical can be  
               mono- or disubstituted by A, Hal, OH, OA, CF<sub>3</sub>, OCF<sub>3</sub>, N(R<sup>5</sup>)<sub>2</sub>,  
               SO<sub>2</sub>A or COOR<sup>5</sup> provided that the heterocyclic radical is not  
               bondend via an N atom,  
 30      Hal      is F, Cl, Br or I,  
       mor      is morpholin-4-yl,  
       Ph      is phenyl,

n is 1, 2, 3, 4, 5 or 6,  
 m is 0, 1, 2, 3, 4, 5 or 6,  
 o is 1, 2, 3, 4, 5, 6 or 7,  
 p is 0, 1, 2, 3 or 4,  
 q is 1, 2, 3 or 4,

and their pharmaceutically tolerable salts and solvates according to at least one of claims 1 to 7, characterized in that

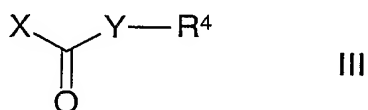
a) a compound of the formula I is liberated from one of its functional derivatives by treating with a solvolysing or hydrogenolysing agent, or

b) for compounds in which Y is a direct bond or  $(CH_2)_n$  in stage 1) a compound of the formula II



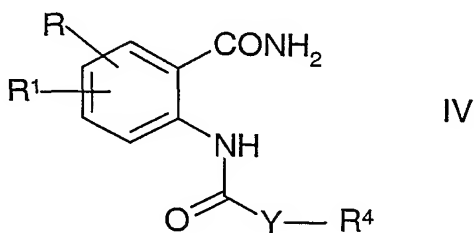
in which

R and R<sup>1</sup> have a meaning indicated in Claim 1,  
 is reacted with a compound of the formula III



in which R<sup>4</sup> has a meaning indicated in Claim 1 and Y is a direct bond or  $(CH_2)_n$ ,

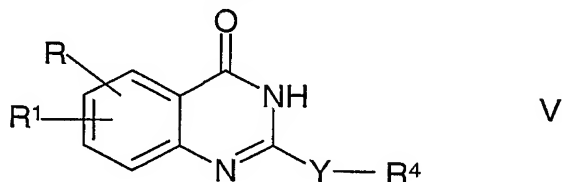
and X is Cl, Br, OH or a reactive esterified OH group followed by converting the cyano group to an amide group by conventional means to give a compound of formula IV



in which R, R<sup>1</sup> and R<sup>4</sup> have a meaning indicated in Claim 1 and Y is a direct bond or (CH<sub>2</sub>)<sub>n</sub>,

in stage 2) a compound of formula IV as indicated above is reacted with a base to give a compound of formula V

5

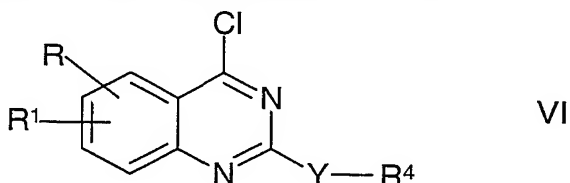


in which R, R<sup>1</sup> and R<sup>4</sup> have a meaning indicated in Claim 1 and Y is a direct bond or (CH<sub>2</sub>)<sub>n</sub>,

10

in stage 3) a compound of formula V as indicated above is reacted with a chlorinating agent to give a compound of formula VI

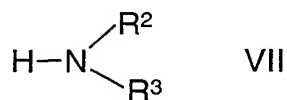
15



in which R, R<sup>1</sup> and R<sup>4</sup> have a meaning indicated in Claim 1 and Y is a direct bond or (CH<sub>2</sub>)<sub>n</sub>,

and in stage 4) a compound of formula VI as indicated above is reacted with a compound of formula VII

20



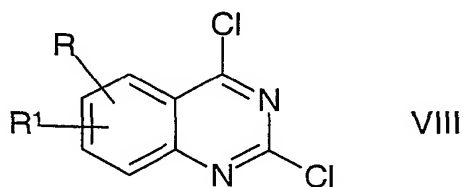
in which R<sup>2</sup> and R<sup>3</sup> or NR<sup>2</sup>R<sup>3</sup> have a meaning indicated in Claim 1,  
or

25

b) for compounds in which Y is NR<sup>5</sup>-(CH<sub>2</sub>)<sub>m</sub>-

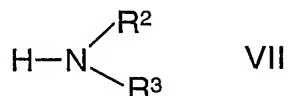
in stage 1) a compound of the formula VIII

30

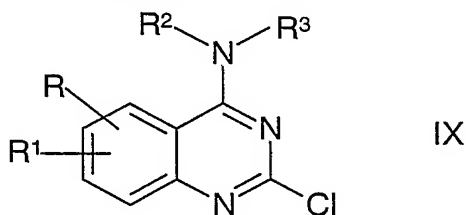


in which

R and R<sup>1</sup> have a meaning indicated in Claim 1,  
is reacted with a compound of formula VII

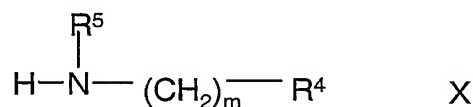


in which R<sup>2</sup> and R<sup>3</sup> or NR<sup>2</sup>R<sup>3</sup> have a meaning indicated in Claim 1, to  
give a compound of formula IX



in which R, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and NR<sup>2</sup>R<sup>3</sup> have a meaning indicated in Claim 1,  
and

in stage 2) a compound of formula IX as indicated above is reacted with  
a compound of formula X



in which R<sup>4</sup>, R<sup>5</sup> and m have a meaning indicated in Claim 1

or

d) a radical R, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and/or R<sup>4</sup> is converted into another radical R,  
R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and/or R<sup>4</sup> by, for example

- reducing a nitro group, sulfonyl group or sulfoxyl group,
- etherifying an OH group or subjecting an OA group to ether cleavage,
- alkylating a primary or secondary amino group,
- partially or completely hydrolysing a CN group,
- cleaving an ester group or esterifying a carboxylic acid radical,
- reacting an aryl bromide, aryl iodide, heteroaryl bromide or heteroaryliodide to give the corresponding coupling products by means of a Suzuki coupling with boronic acids,

- 5
- reacting a iodoquinazoline or bromoquinazoline to give the corresponding coupling products by means of a Stille coupling with allyltributyltin,
  - reacting a iodoquinazoline or bromoquinazoline to give the corresponding coupling products by means of a Heck coupling with acrylates,
  - or carrying out a nucleophilic or electrophilic substitution,
- 10
- or
- a base or acid of the formula I is converted into one of its salts or solvates.

15

9. Compounds of the formula I according to at least one of claims 1 to 7 and their physiologically acceptable salts or solvates as pharmaceutical active compounds.

10. Compounds of the formula I according to claim 9 and their physiologically acceptable salts or solvates as glycoprotein IbIX antagonists.

20

11. Compounds of the formula I according to claim 9 and their physiologically acceptable salts or solvates as glycoprotein IbIX antagonists for the control of thrombotic disorders and sequelae deriving therefrom.

25

12. Pharmaceutical preparation characterized in that it contains at least one compound of the formula I according to at least one of claims 1 to 7 or one of its physiologically acceptable salts or solvates.

30

13. Use of compounds of the formula I according to at least one of claims 1 to 7 and/or their physiologically acceptable salts or solvates for the production of a pharmaceutical preparation for the control of thrombotic

disorders and sequelae deriving therefrom or for use as anti-adhesive substances.

- 5       14. Use of compounds of the formula I according to at least one of claims 1 to 7 and/or their physiologically acceptable salts or solvates for the production of a pharmaceutical preparation for the treatment of illnesses, such as for the prophylaxis and/or therapy of thrombotic disorders, as well as sequelae such as, for example, myocardial infarct, arteriosclerosis, angina pectoris, acute coronary syndromes, peripheral  
10       circulatory disorders, stroke, transient ischaemic attacks, reocclusion/restenosis after angioplasty/stent implantations or as anti-adhesive substances for implants, catheters or heart pacemakers.

15

20

25

30

# INTERNATIONAL SEARCH REPORT

International Application No

PC/EP 01/10705

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D239/94 C07D239/95 C07D403/12 C07D405/12 C07D409/14  
C07D401/12 C07D409/04 A61K31/517 A61P9/10

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, PAJ

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 197 56 388 A (HOECHST MARION ROUSSEL) 24 June 1999 (1999-06-24) the whole document	1-3,5, 8-14
X	CHEMICAL ABSTRACTS, vol. 131, no. 11, 1999 Columbus, Ohio, US; abstract no. 139513m, page 108; XP002184924 abstract & JP 11 209287 A (ONO PHARMA.) 3 August 1999 (1999-08-03) -/--	1-3,5, 9-14

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

\* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*Z\* document member of the same patent family

Date of the actual completion of the international search

6 December 2001

Date of mailing of the international search report

20/12/2001

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Francois, J

## INTERNATIONAL SEARCH REPORT

International Application No

PC1/Er 01/10705

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 120, no. 25, 1994 Columbus, Ohio, US; abstract no. 323450n, AL-TALIB, MAHMOUD: "SYNTHESIS OF 4-DIALKYLAMINOQUINAZOLINES" page 906; column 2; XP002184925 abstract & J. PRAKT. CHEM./CHEM.-ZTG., vol. 335, no. 8, 1993, pages 711-13, ----	1,2,5
A	US 5 658 902 A (KYUNGHYE AHN) 19 August 1997 (1997-08-19) column 1 -column 19; claims; figure IV ----	1-3,5, 8-14
A	WO 99 09986 A (KYOWA HAKKO KOGYO) 4 March 1999 (1999-03-04) cited in the application page 0; table 1 ----	1,2,8-14
A	EP 0 326 329 A (ELI LILLY) 2 August 1989 (1989-08-02) claims -----	1,2,6,8

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 01/10705

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
DE 19756388	A	24-06-1999	DE 19756388 A1	24-06-1999
			AU 2270899 A	12-07-1999
			WO 9932460 A1	01-07-1999
			EP 1040101 A1	04-10-2000
JP 11209287	A	03-08-1999	NONE	
US 5658902	A	19-08-1997	CA 2206046 A1	27-06-1996
			EP 0799221 A1	08-10-1997
			JP 10510834 T	20-10-1998
			WO 9619474 A1	27-06-1996
			US 5773444 A	30-06-1998
WO 9909986	A	04-03-1999	AU 8748798 A	16-03-1999
			WO 9909986 A1	04-03-1999
EP 326329	A	02-08-1989	AT 172725 T	15-11-1998
			AU 632994 B2	21-01-1993
			AU 2874789 A	03-08-1989
			BR 8900365 A	19-09-1989
			CN 1035825 A ,B	27-09-1989
			DE 68928841 D1	03-12-1998
			DE 68928841 T2	12-08-1999
			DK 37089 A	30-07-1989
			EG 19187 A	30-10-1994
			EP 0326329 A2	02-08-1989
			ES 2121737 T3	16-12-1998
			FI 890421 A	30-07-1989
			HU 49791 A2	28-11-1989
			IL 89027 A	31-01-1993
			JP 1226877 A	11-09-1989
			JP 2776864 B2	16-07-1998
			KR 129754 B1	09-04-1998
			MX 14663 A	31-01-1994
			NZ 227733 A	28-08-1990
			PT 89506 A ,B	04-10-1989
			TR 27343 A	13-01-1995
			US 5411963 A	02-05-1995
			ZA 8900623 A	27-12-1989